CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202278Orig1s000

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA:	**202,278**
Sponsor:	**NuPathe, Inc.**
Name:	**Zecuity (sumatriptan iontophoretic transdermal system)**
Proposed Indication:	**Acute treatment of migraine**
Material Submitted:	**NDA resubmission following Complete Response letter issued on 08/29/12**
Receipt Date of Resubmission:	**07/17/12**
Date Review Completed:	**01/10/13**
PDUFA Goal Date:	**01/17/13**
Clinical Reviewer:	**Nushin Todd, MD, PhD Medical Reviewer, DNDP, ODE I**

1. Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval action is recommended for Zecuity (sumatriptan iontophoretic transdermal system) in the treatment of acute migraine. This recommendation is based on review of the resubmitted application. The numerous and significant deficiencies noted in the original submission have been adequately addressed in the resubmission.

1.2 Risk Benefit Assessment

Overall, the benefits derived from Zecuity marginally outweigh its risks of causing numerous adverse events at application site.

The benefits of Zecuity are two-fold; 1) the transdermal route of sumatriptan administration bypasses the gastrointestinal system thereby providing an alternative means of treatment for patients that may not be able to tolerate oral medications and, 2) the technology in the device portion of the product allows for a needleless system of transferring medication through the skin.

Additionally, the effectiveness of Zecuity in the treatment of acute migraine was demonstrated in the single pivotal efficacy study (NP101-007). There was a clear difference between drug and placebo for the primary endpoint of the study: the percentage of patients that were headache-free at 2 hours. A significantly greater proportion of subjects were headache pain free at 2 hours post-treatment in the Zecuity treatment group than in the placebo treatment group. There was also a difference in the percentage of patients that were nausea, photophobia, and phonophobia-free at 2 hours with Zecuity compared to placebo. The differences in these three key secondary endpoints reached statistical significance in favor of the treatment.

The risks of using the product are associated with numerous and significant local adverse events. In the long term safety studies (NP101-008 and NP101-009), over half (57%) of the patients sustained a treatment emergent adverse event. The vast majority of adverse events were related to application site conditions, most commonly pain and pruritus. Skin erythema (ranging from mild to intense severity) at product application site occurred in 81% of patients upon patch removal and persisted in 43% of patients 24 hours after product use.

Additionally, there was a high rate of discontinuation in the long term safety studies (59%). Withdrawal of consent and adverse events were the most common reasons for patients discontinuing participation.

The novelty of the product is arguably overshadowed by its complexity of use and prolonged drug administration time. Application and activation of the product requires several steps which may be complicated for some patients in the throes of a migraine. Also, the timeframe for administration of drug is quite long. Once the product is activated, it takes 4 hours for the medication to be delivered through the skin.

In summary, this drug/device combination product provides a novel route of drug administration for the treatment of acute migraine. Efficacy of the product has been clearly demonstrated in the clinical program. Modifications made to the device portion of the product have mitigated the risks for potential severe burns and scarring that occurred in some patients in the clinical program. Local adverse events from use of the product, however, remain numerous. The product still has the potential to cause local adverse events such as pain, pruritus, erythema, skin discoloration, vesicle formation, and allergic contact dermatitis, to name a few. Patients should be made fully aware of the potential risks for significant local adverse events prior to using the product.

1.3 Recommendation for Postmarket Risk Evaluation and Mitigation Strategies

Routine postmarketing surveillance is appropriate.

1.4 Recommendation for Postmarket Requirements and Commitments

None

2. Introduction and Regulatory Background

Zecuity (sumatriptan iontophoretic transdermal system), is a novel drug/device combination product designed to deliver sumatriptan through the skin via an electric current. It is intended for the acute treatment of migraine in adults.

This new drug application (NDA) was originally submitted on October 29, 2010 in accordance with Section 505(b)(2) of the Food, Drug and Cosmetic Act. The reference for the safety and efficacy of the product is based on GlaxoSmithKline's products: Imitrex® (sumatriptan succinate) Injection (NDA 20080, 1992) and Imitrex® (sumatriptan succinate) Tablets (NDA 20132, 1995).

After review, the original application was found to have numerous deficiencies and a Complete Response letter was issued on August 29, 2011. The following is a summary of some of the major deficiencies noted by the Agency:

Chemistry Manufacturing and Controls (CMC) and Device Issues
The fundamental design of the product was found to be unacceptable. Four major flaws with the design portion of the product were noted that posed potential safety and efficacy concerns. These included lack of uniformity in the distribution of drug on the medication pad, lack of adequate containment of drug and risk of unintentional exposure, lack of proper disposal procedures of the product, and patient usability concerns.

There were additional concerns regarding residual drug, manufacturing processes, specifications and acceptance criteria of components of the patch, analytical methods, stability, and packaging issues. A comprehensive quality risk management was recommended because of the complexity of the product.

Clinical Pharmacology
The sponsor conducted a study comparing the kinetics of the to-be-marketed system with the system actually studied in the clinical trial showing equivalence of the two systems. However, the sponsor's contractor failed to retain samples of

the products used, in violation of the relevant regulations, making it impossible to verify the results of the study. It was recommended that the study be repeated.

Microbiology
There was inadequate proof of antimicrobial effectiveness or microbial control of the finished product.

Biopharmaceutics
Major deficiencies related to the lack of an adequate in vitro method to evaluate drug permeation as a tool to ensure lot-to-lot variability.

Pharmacology/toxicology
The sponsor submitted a 9-month chronic dermal toxicity study in the mini-pig. This toxicology study was deemed inadequate due to an insufficient number of animals, lack of a control group, and inadequate explanation of the chosen dosing interval (one patch/week). There was also a lack of a dermal carcinogenicity study without sufficient justification as to why the study was not conducted.

Clinical
Nine items of clinical concern were highlighted after review of the original application:

- Serious concerns about the potential of the product to cause severe burns and permanent skin lesions
- There was inadequate information regarding the time course and resolution of skin discoloration at product application site
- Serious concerns about the irritation and sensitization potential of the product
- Inadequate description and analysis of skin adverse reactions; re-examination and recoding of local adverse events was needed
- Insufficient information regarding the minimal time between two patch applications, and maximum frequency of use of the product
- Insufficient information to determine the minimal time necessary to safely reapply the product at the same site
- There was a high rate of discontinuation in the long term safety studies with insufficient information on reasons for withdrawal
- Insufficient number of patients exposed for 6 months in the long term safety studies
- Inadequate information to support efficacy of the product in non-white patients

The application was resubmitted on July 17, 2012. In the resubmission, the sponsor addressed the individual deficiencies noted in the Complete Response letter.

The resubmission was reviewed by CMC, devices, clinical pharmacology, microbiology, biopharmaceutics, clinical pharmacology and clinical disciplines within the Food and Drug Administration (FDA). Each section concentrated the focus of their review to their particular field.

3. Review of Clinical Items

A detailed review of the sponsor's responses to the nine clinical deficiencies was conducted. The clinical items of concern have been evaluated individually and are presented below.

CLINICAL ITEM #1

We have serious concerns about the potential for your product to cause severe burns, and permanent skin lesions. You cross-referenced in section 2.1.5.1.4 of your summary of clinical safety the narratives of several cases of patients who experienced permanent skin lesions. For example, patient 127-1197 was noted to have "a slightly raised keloid of 2x1 cm at the application site and some discoloration of the skin in that area" 4.5 months after application of the patch. Another patient (134-2221) was reported as having "skin discoloration at patch site" eighty days post patch application. That patient had two consultations with a dermatologist and one with a plastic surgeon to discuss cosmetic repair for the discoloration. Patient 125-1275 was noted to have "minimal residual mark in area of previous noted blister". We note that you described these events in a section titled "Improper Application". We reject the argument that these lesions can be attributed to "improper application" of the patch (i.e., suggesting the patient and not the product is the cause for the adverse event), as patients in clinical studies were instructed by the Investigational Site Personnel on how to apply the patch. In that setting, the potential for a use of the product different from what was intended, appears to be attributable to product design issues rather than to patient misuse. We consider that clinical trials conditions represent a "best case scenario", and that the potential for skin lesions may be even greater under post-marketing conditions of use. We also note that there were 3 adverse event reports (0.4%) of severe burns, and 2 reports of moderate burns (0.3%) in long term safety studies, and one report of "mild scar". In addition, we cannot rule out that your database includes additional cases of permanent skin lesions that were not described in your summary of clinical safety. Unless you can provide evidence that cases of significant administration site adverse events (e.g., burn, scar, discoloration or abnormal pigmentation) in your database ultimately resolved, we believe that the risk of skin lesions (in particular with permanent sequelae) is not justified by the benefits of the product.

Review of Resubmission

Review of the sponsor's response to clinical item #1 is primarily focused on the adverse events of application site burns and scarring incurred from the use of NP101 transdermal patch. Other significant administration site adverse events such as discoloration, bruising, vesicle formation, skin irritation, etc., are discussed in detail in the review of the sponsor's responses to subsequent clinical items.

In the long term safety studies, 5 subjects (0.8%, 5/662) sustained burns at application site from use of NP101 patch. Of the 5 subjects, 2 had burns of moderate intensity and 3 sustained severe burns. On average, it took 43 days for

healing of burn (ranging from 2 to 80 days). Residual scarring of the skin occurred in 3 of the 5 subjects.

There were a total of 3 cases of scarring in the long term safety studies. All cases of scarring were the permanent sequelae of burns. Review of all application site adverse events (reviewed in subsequent clinical items) revealed that scarring was the only permanent skin lesion in clinical studies.

In the resubmission, the sponsor did not specifically discuss the case histories of the 5 subjects who sustained burns and scars. Rather, burn and scar cases were discussed as part of a subgroup of adverse events associated with patch "misapplication".

I reviewed the resubmission (clinical study reports, case report forms, etc.,) and identified the 5 subjects with burns in the long term safety studies. The following is a synopsis of the information obtained from reviewing the cases:

- Subject 134-2051: (Patch ID 26111; burn event with 5th patch) Subject reported dime-sized burn equal to metal conductor on patch. *Site CRF comment*: cathode side medication pad was not properly transferred. *Outcome*: application site burn, recovered in 2 days. Application site scar, ongoing. Subject completed the study.

- Subject 134-2221: (Patch ID 20426; burn event with 1st patch) *Site CRF comment*: medication pads were not properly transferred onto the patch resulting in electrodes being placed directly against the subject's skin. *Outcome*: application site burn, recovered in 80 days. Application site scar, ongoing. Subject discontinued due to application site burn.

- Subject 134-2278: (Patch ID 17888; burn event with 5th patch) Subject noticed pads were not attached during treatment. *Outcome*: application site burn, recovered in 40 days. Subject completed the study.

- Subject 155-2017: (Patch ID 18791; burn event with 6th patch) *subject diary comment*: "patch left a contact burn on my left upper arm. The burn is oval and put a small hole in my skin". *Site CRF comment*: keloid scar left upper arm. *Outcome*: application site burn, recovered in 73 days. Application site scar, ongoing. Subject completed the study.

- Subject 158-2076: (Patch ID 22306; burn event with 3rd patch) *subject diary comment*: "pad was off and caused a 'pit' like burn. One of the lubricated pads wasn't attached and burn a 'hole' was pretty significant on right arm". *Site CRF comment*: electrical burn, 1.3 cm. *Outcome*: application site burn, recovered in 21 days. Subject discontinued from the study.

The sponsor attributed all cases of burns and scars to "misapplication" of patch. The term "misapplication" was used by the sponsor to describe events that occurred when the medication pad(s) were missing or when the pads did not properly transfer to cover one or both electrodes completely on the patch. When these patches were activated, it caused several instances of intense skin erythema with burns and blistering.

As discussed in Clinical Item #1, the term patch "misapplication" gives the impression that the patient and not the product is the cause of the adverse event. A more appropriate term to use perhaps is "misassembled" patch.

A total of 10,213 NP101 or placebo patches were applied on subjects in the combined Phase 3 clinical studies. From the over 10,000 patches applications, there were 16 documented cases of patch misassembly (15 subjects). The 16 cases were distributed as follows:

- 3 cases in study NP101-007 (including one with placebo patch)
- 13 cases in NP101-009 (including one subject with 2 misassembled patches)

Of the 16 cases, 3 patches did not result in any adverse events. In 6 cases, subjects experienced adverse events of burns and/or scar formation (including one placebo subject in study NP101-007). The remainder of the cases included application site pain, irritation, vesicles, bruising and erosion.

In order to fully evaluate the problem of misassembled patches, the sponsor contracted with an engineering firm, (b) (4) to perform analytical testing on a subset of NP101 patches used in the clinical trials.

The sponsor retrieved patches used in the clinical program including 11 patches in the long term studies that were reported as being misapplied as well as other used patches associated with adverse events of application site discoloration, application site vesicles, and application site skin irritation score of 4 (intense redness with blisters or broken skin). Included in the retrieved patches were the 5 patches that were associated with the cases of burns listed above. In all, 57 patches were sent to (b) (4) for analysis.

Patches underwent analyses involving optical microscopy and scanning electron microscopy with energy dispersive spectroscopy. The following are conclusions from the analyses:

- The majority of patches that were identified as having misaligned, missing, or incorrectly transferred pads had areas of light brown discoloration that were associated with localized depletion of chloride on the electrode surface. The regions of the electrode surface that most commonly exhibited this discoloration were crescent-shaped areas at the edge and circular areas in the interior. This type of discoloration and concomitant

chloride depletion appears to be one diagnostic of a patch misapplication. Samples of patches used in the clinical setting and known to have had proper application and no reported adverse events did not exhibit the same type of discoloration and localized depletion of surface chloride levels that were seen in the misapplication group.

- The depletion of chloride at the electrode surface is likely related to an elevated level of electrochemical activity in a localized area, which in turn suggests that these discolored areas were associated with levels of increased electrical current density relative to the non-depleted areas of the electrode. As the patches in this group were those associated with burns and scars, this finding underscores the importance of proper pad alignment and electrode coverage to minimize the formation of these localized areas of increased current density.

- In addition, samples of patches associated with other types of adverse events in the clinical setting, including application site irritation, vesicles, and discoloration, did not exhibit areas of discoloration or localized chloride depletion as found in the misapplication group, with the exception of 2 patches from Study NP101-009. Based on the analysis for these two cases (Subject 158-2076, AE of skin irritation of "4" and Subject 140-2078, AE of application site vesicles), the sponsor considers them to be patch misapplications also. Subject 158-2076 was reported to have a known patch misapplication and therefore presumably had two misapplications.

- Samples of patches used in the clinical setting and known to have had proper application and no reported adverse events did not exhibit the same type of discoloration and localized depletion of surface chloride levels that were seen in the misapplication group.

After completion of the long term safety studies, the sponsor modified the patch with the aim of preventing occurrences of patch activation when pads were either misaligned or missing. The change in the patch system incorporated a "Pad Detection System" (PDS) whereby NP101 patches that did not have the electrodes completely and properly covered would not activate.
The PDS consists of sensing elements in the form of (b) (4) . The drug and salt pads on the patch have to be properly aligned against all (b) (4) in order for the patch to be activated.

Clinical testing of the modified patches incorporating the PDS was conducted in clinical studies NP101-025 and NP101-026. A total of 647 modified patches were tested in the combined studies with reportedly 100% effectiveness in detecting misaligned or absent medication pads and preventing patch activation. The following is a brief overview of the two studies:

- Study NP101-025: study verifying the functioning of the PDS design; 507 applied patches conducted in 26 healthy subjects.

- Study NP101-026: Bioequivalence study comparing the modified NP101 patch incorporating the PDS design to the original patch. A total of 32 healthy subjects received at least one NP101 patch application in the study; 140 patches with the PDS were applied during PDS verification testing.

The sponsor believes the risk of burns and subsequent scars due to patch misassembly have been effectively addressed and should no longer occur because of the modifications made to the patch. The new patch, incorporating the PDS design identifies incorrectly assembled or absent medication pad(s) and prevents patch activation.

In conclusion, the sponsor has adequately addressed the serious concerns of burns and potential permanent scarring of skin that occurred in the clinical trials from misassembled patches. Modifications made to the patch, specifically, the incorporation of the Pad Detection System, mitigate the safety risk of burns and subsequent permanent skin lesions such as scarring.

CLINICAL ITEM #2

Site discoloration was reported as an adverse event in 4.3% of patients in long-term safety studies. You have not provided sufficient information to allow us to determine the time course and reversibility of the discoloration. Please provide that information. Permanent discoloration of the skin would typically not represent an acceptable side effect for a product indicated for the acute treatment of migraine.

Review of Resubmission

The sponsor re-examined patch application site adverse events related to skin discoloration in the three Phase 3 clinical studies (NP101-007, -008, and -009). Adverse events were recoded to eliminate non-specific terms and updated datasets were provided. Follow-up information was also obtained for subjects whose skin conditions were on-going at the time of the original submission and the 120-Day Safety Update.

Based on recoding of adverse events and data updates, there was an increase in the total number of subjects with skin discoloration at site of patch application in the Phase 3 clinical studies. In the 120-Day Safety Update submission, 4.4% (29/662) of subjects had an adverse event of skin discoloration in the long term safety studies. In the resubmitted data, the number of subjects with skin discoloration at patch application site increased to 5.1% (34/662).

The majority of skin discoloration events were mild or moderate in intensity. One subject had skin discoloration described as severe, which was associated with allergic contact dermatitis. Adverse events, including skin discoloration, in the long term safety studies are summarized by severity in Table 1.

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Table 1 Summary of Treatment Emergent Adverse Events in Long Term Safety Studies (NP101-008 and NP101-009)

System Organ Class	Number (%) of Subjects Reporting Event NP101 (N=662)			
MedDRA Preferred Term (Recoded AEs)	Mild	Moderate	Severe	Total
Subjects with at least one TEAE	154 (23.3)	159 (24.0)	66 (10.0)	379 (57.3)
General disorders and administration site conditions				
Application site anaesthesia	0	1 (0.2)	0	1 (0.2)
Application site bruising	10 (1.5)	2 (0.3)	1 (0.2)	13 (2.0)
Application site burn	0	2 (0.3)	3 (0.5)	5 (0.8)
Application site discharge	0	0	1 (0.2)	1 (0.2)
Application site discolouration	27 (4.1)	6 (0.9)	1 (0.2)	34 (5.1)
Application site discomfort	35 (5.3)	7 (1.1)	1 (0.2)	43 (6.5)
Application site dryness	31 (4.7)	1 (0.2)	0	32 (4.8)
Application site erosion	0	3 (0.5)	0	3 (0.5)
Application site erythema	3 (0.5)	1 (0.2)	2 (0.3)	6 (0.9)
Application site excoriation	2 (0.3)	0	0	2 (0.3)
Application site exfoliation	16 (2.4)	1 (0.2)	0	17 (2.6)
Application site hyperaesthesia	3 (0.5)	2 (0.3)	1 (0.2)	6 (0.9)
Application site induration	0	0	1 (0.2)	1 (0.2)
Application site inflammation	1 (0.2)	0	0	1 (0.2)
Application site irritation	10 (1.5)	6 (0.9)	7 (1.1)	23 (3.5)
Application site mass	0	1 (0.2)	0	1 (0.2)
Application site oedema	0	3 (0.5)	0	3 (0.5)
Application site pain	60 (9.1)	60 (9.1)	11 (1.7)	131 (19.8)
Application site papules	2 (0.3)	1 (0.2)	0	3 (0.5)
Application site paraesthesia	26 (3.9)	4 (0.6)	1 (0.2)	31 (4.7)
Application site pruritus	70 (10.6)	30 (4.5)	7 (1.1)	107 (16.2)
Application site rash	3 (0.5)	0	0	3 (0.5)
Application site scar[a]	3 (0.5)	0	0	3 (0.5)
Application site swelling	7 (1.1)	1 (0.2)	0	8 (1.2)
Application site urticaria	1 (0.2)	1 (0.2)	0	2 (0.3)
Application site vesicles	6 (0.9)	10 (1.5)	3 (0.5)	19 (2.9)
Application site warmth	13 (2.0)	2 (0.3)	0	15 (2.3)

[a] Associated with patch misapplication

(Source: Sponsor's resubmission; Summary of Clinical Safety, Section 2.7.4.2.1.1.3.2, Table 16)

There were no cases of skin discoloration due to patch misapplication. All cases of skin discoloration eventually resolved. Mean time to resolution, however, was quite long. On average, it took 71 days for skin discoloration to resolve.

The sponsor consulted with two dermatologists to review the cases of skin discoloration: (b) (4) [redacted]. It was concluded by the dermatologists that the cases of discoloration were "consistent with hyperpigmentation seen after external insult, such as that caused by any transdermal system; and represent a transient aspect of the healing process and not a permanent pigmentary change".

In summary, skin discoloration at site of patch application occurred in 5% of subjects in the overall safety population. No cases were attributable to patch misapplication. While there were no cases of permanent skin discoloration from patch use, the mean time to resolution, however, was quite long. On average, it took 2.5 months (71 days) for skin discoloration to resolve.

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CLINICAL ITEM #3

We are concerned about the significant irritation and sensitization potential of your product. In long-term safety studies, bruising was reported as an adverse event in 2.4% of patients, and vesicles were reported in 2.4% of patients. In addition, intense redness at the site of treatment was observed in 6% of patients 4 hours post-treatment, and in 2.7% of patients 24 hours after treatment. Blisters or broken skin were observed in 0.5% of patients 24 hours after treatment. Unless these findings can be dismissed as non-clinically significant, we do not believe that the benefits of the product justify the side effects at the site of administration.

Review of Resubmission

The sponsor re-examined all patch application site adverse events in the Phase 3 clinical studies. Changes were made in coding of adverse event preferred terms to allow for more specific terms to be used for events initially coded as "adverse drug reaction" or "application site reaction". Updated data with coding changes and follow-up information of unresolved adverse events were provided in the resubmission.

In many instances, the sponsor combined data from the three Phase 3 studies (the efficacy study NP101-007, and the two long term safety studies NP101-008 and -009). For example, when discussing aspects of application site adverse events of clinical concern such as severity of events, time to resolution and associated events, data were incorporated into an overall safety population of the combined Phase 3 studies.

The combining of safety data from a single dose study with a chronic study, as conducted by the sponsor, is problematic as the overall incidence of adverse events is typically underestimated. Therefore, in reviewing the resubmission, I avoided evaluating the single dose study with the chronic studies. Rather, the review assessed safety results of these studies separately with focus placed on the long term safety studies.

Application site bruising

In the updated long term safety studies, bruising at patch application site was reported by 13 of 662 subjects (2.0%). Severity of bruising was reported as mild in 10 subjects (1.5%), moderate in 2 subjects (0.3%), and severe in 1 subject (0.2%). Summary of treatment emergent adverse events by severity, including bruising, at patch application site is presented in Table 2.

Table 2 Summary of Treatment Emergent Adverse Events in Long Term Safety Studies (NP101-008 and NP101-009) (Recoded AEs)

System Organ Class	Number (%) of Subjects Reporting Event			
	NP101 (N=662)			
MedDRA Preferred Term (Recoded AEs)	Mild	Moderate	Severe	Total
Subjects with at least one TEAE	154 (23.3)	159 (24.0)	66 (10.0)	379 (57.3)
General disorders and administration site conditions				
Application site anaesthesia	0	1 (0.2)	0	1 (0.2)
Application site bruising	10 (1.5)	2 (0.3)	1 (0.2)	13 (2.0)
Application site burn	0	2 (0.3)	3 (0.5)	5 (0.8)
Application site discharge	0	0	1 (0.2)	1 (0.2)
Application site discolouration	27 (4.1)	6 (0.9)	1 (0.2)	34 (5.1)
Application site discomfort	35 (5.3)	7 (1.1)	1 (0.2)	43 (6.5)
Application site dryness	31 (4.7)	1 (0.2)	0	32 (4.8)
Application site erosion	0	3 (0.5)	0	3 (0.5)
Application site erythema	3 (0.5)	1 (0.2)	2 (0.3)	6 (0.9)
Application site excoriation	2 (0.3)	0	0	2 (0.3)
Application site exfoliation	16 (2.4)	1 (0.2)	0	17 (2.6)
Application site hyperaesthesia	3 (0.5)	2 (0.3)	1 (0.2)	6 (0.9)
Application site induration	0	0	1 (0.2)	1 (0.2)
Application site inflammation	1 (0.2)	0	0	1 (0.2)
Application site irritation	10 (1.5)	6 (0.9)	7 (1.1)	23 (3.5)
Application site mass	0	1 (0.2)	0	1 (0.2)
Application site oedema	0	3 (0.5)	0	3 (0.5)
Application site pain	60 (9.1)	60 (9.1)	11 (1.7)	131 (19.8)
Application site papules	2 (0.3)	1 (0.2)	0	3 (0.5)
Application site paraesthesia	26 (3.9)	4 (0.6)	1 (0.2)	31 (4.7)
Application site pruritus	70 (10.6)	30 (4.5)	7 (1.1)	107 (16.2)
Application site rash	3 (0.5)	0	0	3 (0.5)
Application site scar[a]	3 (0.5)	0	0	3 (0.5)
Application site swelling	7 (1.1)	1 (0.2)	0	8 (1.2)
Application site urticaria	1 (0.2)	1 (0.2)	0	2 (0.3)
Application site vesicles	6 (0.9)	10 (1.5)	3 (0.5)	19 (2.9)
Application site warmth	13 (2.0)	2 (0.3)	0	15 (2.3)

[a] Associated with patch misapplication

(Source: Sponsor's resubmission; Summary of Clinical Safety, Section 2.7.4.2.1.1.3.2, Table 16)

There were no cases of bruising that resulted in a permanent skin lesion. On average, it took 9 days for resolution of bruising. Three cases of bruising were associated with allergic contact dermatitis. Of note, the incidence of bruising associated with patch use increased with age with a marked spike in bruising occurring in subjects >60 years of age (data not shown).

The sponsor attributed bruising to the design and material used for the NP101 patch that made it difficult to depress the activation button on the patch. According to the sponsor, "some subjects pressed the start button very firmly in order to activate the patch, which could have accounted for the bruising".

While the long term safety studies were ongoing, modifications were made to the design and materials used for the NP101 patch including changes to the dome portion of the patch which houses the activation button. The changes to the patch allowed for less pressure to be applied when activating the patch.

The incidence of bruising decreased with modifications to the dome portion of the patch. A total of 9,978 patches were used in the Phase 3 studies of which 8,177 contained the old dome material and 1,801 patches contained the new material. Bruising was reported by 1.6% of subjects using the old dome material and by 0.3% of subjects using the new patch (data not shown).

Application site vesicle formation

Vesicle formation at patch application site was reported by 19 of 662 subjects (2.9%) in the updated long term safety studies (Table 2). Severity of vesicles was reported as mild in 6 subjects (0.9%), moderate in 10 subjects (1.5%), and severe in 3 subjects (0.5%). Seven of 662 subjects (1.1%) discontinued in the long term studies due to adverse event of vesicles. There were no cases of vesicles that resulted in a permanent skin lesion. On average, it took 2.7 days for resolution of vesicles.

Skin irritation assessments

Skin irritation assessments were conducted by subjects at specified times from removal of NP101 patch to resolution of skin condition. Subjects who reported a skin irritation score of ≥1 performed daily skin examinations until resolution of condition and return of skin irritation score to 0.

In the updated long term safety studies, records of skin assessment scores at 4, 6, 12, and 24 hours after patch activation as well as daily until resolution of skin erythema were re-examined. The final study data incorporated an additional 2,000 patch uses that were not available at the time of the original NDA submission.

Upon patch removal (4 hours post patch activation) 81% (7634/9383) of subjects reported having some degree of erythema, ranging from minimal redness to intense redness with blisters or broken skin (erythema score of 1 to 4). By 24 hours, 43% (3975/9312) of subjects had erythema scores of ≥1. A summary of subject skin assessment by time point (within 24 hours after patch activation) is presented in Table 3.

Intense redness at the site of treatment was observed in 5% of subjects 4 hours post-treatment, and in 2% of subjects 24 hours after treatment. Blisters or broken skin were observed in 0.5% of subjects 24 hours after treatment. The sponsor reported that of the 42 application sites (34 subjects) with blisters or broken skin (erythema score of 4) at 24 hours, 27 cases were associated with allergic contact dermatitis and 5 were associated with patch "misapplication" (when medication pads were not properly transferred to completely cover one or both electrodes on the patch).

Table 3 Summary of Skin Assessment by Time Point within 24 Hours after Patch Application in Long Term Safety Studies

	Time Point Post Patch Application (N=662)			
Skin Assessment Scores	**4 Hours**	**6 Hours**	**12 Hours**	**24 Hours**
Number of patches scored	9383	9517	9388	9312
Distribution, n (%)[a]				
No redness	1749 (18.6)	2531 (26.6)	3533 (37.6)	5337 (57.3)
Minimal redness	2836 (30.2)	2859 (30.0)	2892 (30.8)	1834 (19.7)
Moderate redness	4310 (45.9)	3747 (39.4)	2693 (28.7)	1937 (20.8)
Intense redness with or without swelling	453 (4.8)	350 (3.7)	239 (2.5)	162 (1.7)
Intense redness with blisters or broken skin	35 (0.4)	30 (0.3)	31 (0.3)	42 (0.5)
Missing[b]	10	9	10	12
Mean (SD)	1.4 (0.85)	1.2 (0.89)	1.0 (0.89)	0.7 (0.89)
Median	2.0	1.0	1.0	0.0
Minimum, Maximum	0, 4	0, 4	0, 4	0, 4

[a] The denominator is the total number of patches with a score at the respective time point.
[b] Missing is not included in the denominator.
Skin assessment scores: 0 = no redness; 1 = minimal redness; 2 = moderate redness; 3 = intense redness with or without swelling; 4 = intense redness with blisters or broken skin.

(Source: Sponsor's resubmission; Summary of Clinical Safety, Section 2.7.4.4.3.2.1, Table 34)

Resolution of erythema ranged from 0.2 days to 164 days (mean of 3 days). Mean time to resolution of erythema was 2.7 days (ranging from 0.2 days to 164 days. This was based on a total of 9287 patches for which complete data was available.

In summary, the sponsor has provided convincing evidence of the decrease in bruising events with the modified patch compared to the old patch. It is also reassuring to find that there were no cases of permanent sequelae from bruising, vesicle formation or skin irritation events from patch use. However, the sponsor has not provided compelling evidence refuting the significant irritation potential of the product as noted in the considerable number of local side effects from the use of the product. While there were no cases of permanent skin lesions from bruising, vesicle formation or erythema from patch use, the time to resolution of skin lesions was extremely long in some cases (up to 164 days for skin irritation to resolve). Additionally, in the long term safety studies, over half of the subjects (57%) had a treatment emergent adverse event with the use of the patch. In 10% of these cases, the incidences were severe in intensity. Overall, the potential for long-lasting local adverse events with patch use is significant and warrants careful thought when considering the potential benefit that it may provide.

CLINICAL ITEM #4

We were not able to estimate the exact incidence of adverse events because they were often reported by non-specific terms such as "site reactions" or "adverse drug reactions". For your updated integrated summary of safety, you need to re-examine and recode adverse events that were described using non-specific terms, and also provide updated datasets.

Review of Resubmission

Adverse events in the three Phase 3 clinical studies were re-reviewed and recoded. Changes were also made to the safety database after re-examination of the safety data and follow-up data obtained for events that were unresolved at the time of individual study database lock.

The sponsor forwarded adverse events in the clinical program to (b) (4), a company specializing in coding and versioning of data for drug safety and clinical trials. (b) (4) reviewed the coding of "General Disorders and Administration Site Conditions" and provided the sponsor with recommendations for changes to adverse event preferred terms.

Based on (b) (4) recommendation, symptoms of skin adverse events were recoded to report individual adverse event symptoms rather than syndromes. The sponsor reported that this resulted in an increase in the overall number of application site conditions as single adverse events were reported by investigators using multiple terms.

The following are the changes made to coding of adverse events:

- Events identified as "atypical" or "triptan sensations" were recoded based on the original verbatim term.

- Potential cases of allergic contact dermatitis (ACD) reported by the investigator using terms such as suspected delayed hypersensitivity, delayed hypersensitivity, and contact dermatitis were recoded to the preferred term "dermatitis contact" and listed under System Organ Class (SOC) of Skin and Subcutaneous Tissue Disorders".

- The term "application site reaction" was eliminated and application site events were recoded based on the original descriptive terms such as:
    - Burn = Burn
    - Burning sensation (painful) = Pain
    - Burning sensation (non-painful) = Discomfort
    - Burning sensation (without descriptor) =Application Site Irritation
    - Stinging (painful) = Pain

- Stinging (non-painful) = Discomfort
- Stinging (without descriptor) = Pain
- Skin irritation = Irritation
- Tightness = Discomfort
- Tingling = Paresthesia

- Adverse events that had multiple descriptive terms were split and recoded to the individual descriptive terms that existed in the verbatim term (e.g., Patch Application Site Disorder, "PASD" – Hot and Pain was changed to PASD – Hot and PASD – Pain).

- Adverse events involving *skin irritation = 4*, when multiple descriptive terms existed in the original verbatim term, they have now all been split and recoded to include the individual descriptive terms that existed in the verbatim, e.g., *erythema and blisters*; or *erythema, warmth, and vesicles*, etc., in the same manner as for lower skin irritation scores. In the few cases where the verbatim term was only *skin irritation = 4* without any other descriptive terms, this term has been retained even though it does not contain an event.

- Resolution dates for unresolved adverse events for 3 subjects (2 subjects in study NP101-007 and 1 subject in study NP101-008) as of database locks were provided.

- Re-examination of safety data and additional follow-up data from study sites resulted in recoding and database changes for the following cases:
  - Study NP101-007: adverse event of "application site scar" was added to subject #127-1197 (NP101 patch group); adverse event term of "burn" was changed to "discoloration" for subject #142-1416 (NP101 patch group); adverse event of "pain" was changed to "burn" in subject #100-1203 (placebo group).
  - Study NP101-009: adverse event of "discoloration" was changed to "scar" in subject #134-2221.

Controlled efficacy study (NP101-007)

In the original submission, 50% of subjects on active drug and 44% of subjects in the placebo group experienced an adverse event. The placebo group had a patch applied to the skin and had electrical current delivered which likely explained the high event rate in this group. The vast majority of adverse events were related to the patch application site. Pain at the application site was reported by 23% of NP10-treated subjects and 15% of placebo-treated subjects. Summary of the original coding of treatment emergent adverse events is reprinted below from the sponsor's resubmission.

Table 4 Summary of Treatment-Emergent Adverse Events Reported by ≥1% of Subjects in Either Treatment Group – Study NP101-007 (Safety Population) (Original AE Coding)

	Number (%) of Subjects Reporting Event			
	NP101 (N=234)		Placebo (N=235)	
MedDRA Preferred term (Original AE Coding)	All	Related	All	Related
Total subjects with at least one treatment-emergent AE	117 (50.0)	114 (48.7)	103 (43.8)	100 (42.6)
Application site pain	54 (23.1)	54 (23.1)	34 (14.5)	34 (14.5)
Application site paraesthesia	28 (12.0)	28 (12.0)	44 (18.7)	44 (18.7)
Application site pruritus	18 (7.7)	18 (7.7)	16 (6.8)	16 (6.8)
Application site reaction	16 (6.8)	16 (6.8)	13 (5.5)	13 (15.5)
Application site warmth	9 (3.8)	9 (3.8)	4 (1.7)	4 (1.7)
Application site discoloration	5 (2.1)	5 (2.1)	3 (1.3)	3 (1.3)
Adverse drug reaction	4 (1.7)	4 (1.7)	0	0
Nausea	3 (1.3)	3 (1.3)	0	0
Somnolence	2 (0.9)	2 (0.9)	3 (1.3)	3 (1.3)

(Source: Sponsor's resubmission; Summary of Clinical Safety, Section 2.7.4.2.1.1.2.1, Table 12)

With the recoding of adverse events, there was a slight increase in overall treatment emergent adverse events for both NP101-treated group (from 50% to 51%) and placebo treated group (from 44% to 45%) (Table 5). Application site pain was the largest reported adverse event in both groups (26% in NP101-treated group and 17% in placebo-treated group).

Table 5 Summary of Treatment-Emergent Adverse Events Reported by ≥1% of Subjects in Either Treatment Group – Study NP101-007 (Safety Population) (Recoded Adverse Events)

	Number (%) of Subjects Reporting Event	
MedDRA Preferred term (Recoded AEs)	NP101 (N=234)	Placebo (N=235)
Total subjects with at least one treatment-emergent AE	119 (50.9)	105 (44.7)
Application site pain	61 (26.1)	39 (16.6)
Application site paraesthesia	20 (8.5)	38 (16.2)
Application site pruritus	19 (8.1)	17 (7.2)
Application site warmth	15 (6.4)	6 (2.6)
Application site discomfort	13 (5.6)	14 (6.0)
Application site irritation	9 (3.8)	5 (2.1)
Application site discoloration	6 (2.6)	3 (1.3)
Nausea	3 (1.3)	0
Somnolence	2 (0.9)	3 (1.3)

(Source: Sponsor's resubmission; Summary of Clinical Safety, Section 2.7.4.2.1.1.2.1, Table 13)

Long term safety studies (NP101-008 and NP101-009)

In the 120-Day Safety Update Report, 57% (379/662) of subjects in the long term trials experienced at least one treatment emergent adverse event. Most of these events were related to application site conditions. The most common adverse events were pain and pruritus. Application site pain was reported by 20% (132/662) of subjects and pruritus by 16% (107/662) (Table 6).

Table 6 Summary of Treatment Emergent Adverse Events Experienced by ≥1.0% of Subjects Treated With NP101 - Safety Population (Studies NP101-008 and NP101-009) (Original Adverse Events Coding)

	Number (%) of Subjects (N=662)	
System Organ Class MedDRA Preferred Term (Original AE Coding)	**All AEs Original NDA**	**All AEs Final Study Data**
Subjects with at least one TEAE	348 (52.6)	379 (57.3)
Gastrointestinal disorders		
Nausea	10 (1.5)	10 (1.5)
General disorders and administration site conditions		
Adverse drug reaction	5 (0.8)	7 (1.1)
Application site bruising	16 (2.4)	18 (2.7)
Application site discoloration	26 (3.9)	35 (5.3)
Application site dryness	29 (4.4)	32 (4.8)
Application site exfoliation	16 (2.4)	17 (2.6)
Application site hyperaesthesia	11 (1.7)	11 (1.7)
Application site hypersensitivity	28 (4.2)	31 (4.7)
Application site irritation	8 (1.2)	11 (1.7)
Application site pain	117 (17.7)	132 (19.9)
Application site paraesthesia	34 (5.1)	34 (5.1)
Application site pruritus	101 (15.3)	107 (16.2)
Application site reaction	38 (5.7)	38 (5.7)
Application site swelling	7 (1.1)	8 (1.2)
Application site vesicles	16 (2.4)	17 (2.6)
Application site warmth	12 (1.8)	15 (2.3)
Infections and infestations		
Gastroenteritis viral	5 (0.8)	7 (1.1)
Influenza	5 (0.8)	8 (1.2)
Nasopharyngitis	13 (2.0)	16 (2.4)
Sinusitis	8 (1.2)	8 (1.2)
Upper respiratory tract infection	23 (3.5)	29 (4.4)

(Source: Sponsor's resubmission; Summary of Clinical Safety, Section 2.7.4.2.1.1.3.1, Table 15)

In the resubmission, the sponsor provided a summary table of treatment emergent adverse events reported as application site conditions by severity based on recoding of adverse events and updated data (Table 7).

Table 7 Summary of Treatment-Emergent Adverse Events Reported as Application Site Conditions – Studies NP101-008 and NP101-009 (Safety Population)(Recoded AEs)

System Organ Class	Number (%) of Subjects Reporting Event			
	NP101 (N=662)			
MedDRA Preferred Term (Recoded AEs)	Mild	Moderate	Severe	Total
Subjects with at least one TEAE	154 (23.3)	159 (24.0)	66 (10.0)	379 (57.3)
General disorders and administration site conditions				
Application site anaesthesia	0	1 (0.2)	0	1 (0.2)
Application site bruising	10 (1.5)	2 (0.3)	1 (0.2)	13 (2.0)
Application site burn	0	2 (0.3)	3 (0.5)	5 (0.8)
Application site discharge	0	0	1 (0.2)	1 (0.2)
Application site discolouration	27 (4.1)	6 (0.9)	1 (0.2)	34 (5.1)
Application site discomfort	35 (5.3)	7 (1.1)	1 (0.2)	43 (6.5)
Application site dryness	31 (4.7)	1 (0.2)	0	32 (4.8)
Application site erosion	0	3 (0.5)	0	3 (0.5)
Application site erythema	3 (0.5)	1 (0.2)	2 (0.3)	6 (0.9)
Application site excoriation	2 (0.3)	0	0	2 (0.3)
Application site exfoliation	16 (2.4)	1 (0.2)	0	17 (2.6)
Application site hyperaesthesia	3 (0.5)	2 (0.3)	1 (0.2)	6 (0.9)
Application site induration	0	0	1 (0.2)	1 (0.2)
Application site inflammation	1 (0.2)	0	0	1 (0.2)
Application site irritation	10 (1.5)	6 (0.9)	7 (1.1)	23 (3.5)
Application site mass	0	1 (0.2)	0	1 (0.2)
Application site oedema	0	3 (0.5)	0	3 (0.5)
Application site pain	60 (9.1)	60 (9.1)	11 (1.7)	131 (19.8)
Application site papules	2 (0.3)	1 (0.2)	0	3 (0.5)
Application site paraesthesia	26 (3.9)	4 (0.6)	1 (0.2)	31 (4.7)
Application site pruritus	70 (10.6)	30 (4.5)	7 (1.1)	107 (16.2)
Application site rash	3 (0.5)	0	0	3 (0.5)
Application site scar[a]	3 (0.5)	0	0	3 (0.5)
Application site swelling	7 (1.1)	1 (0.2)	0	8 (1.2)
Application site urticaria	1 (0.2)	1 (0.2)	0	2 (0.3)
Application site vesicles	6 (0.9)	10 (1.5)	3 (0.5)	19 (2.9)
Application site warmth	13 (2.0)	2 (0.3)	0	15 (2.3)

[a] Associated with patch misapplication

(Source: Sponsor's resubmission; Summary of Clinical Safety, Section 2.7.4.2.1.1.3.2, Table 16)

Over half of all subjects (57%, 379/662) sustained a treatment emergent adverse event in the long term studies. Adverse events of severe intensity were reported by 10% (66/662) of subjects in the studies. Another 24% (159/662) reported adverse events of moderate intensity. Application site pain and pruritus were the most commonly reported adverse events. Pain was reported by 20% (131/662) of subjects and pruritus by 16% (107/662) of subjects.

Dermatitis contact was the most frequently reported severe adverse event in the long term safety studies. There were a total of 33 cases (5.0%) of dermatitis contact reported. Of these, 12 cases (1.8%) were of severe intensity. Another 11 reports of dermatitis contact (1.7%) were of moderate intensity, and 10 cases (1.5%) were mild in intensity.

In conclusion, the sponsor has re-examined and recoded adverse events that were originally described using non-specific terms. Events such as “site reactions” or “adverse drug reactions” have been removed in the recoding. Additionally, ongoing adverse events at the time of the 120-Day Safety Update were followed up and database updates were made.

APPEARS THIS WAY ON ORIGINAL

CLINICAL ITEM #5

You proposed a labeling statement that [redacted] (b) (4) and that " [redacted] (b) (4) ." There is insufficient information to support application of a second patch after 2 hours, or to support use of more than 2 patches per month, as there was no specific analysis of patients using the treatment under these conditions in your NDA, and limited information of patients treating more than 2 attacks per month, on average. You need to submit sufficient and adequate safety information for patients using the product under the conditions proposed to be described in labeling, e.g., using a second patch after 2 hours, or using up to the maximum recommended frequency of use.

Review of Resubmission

Review of the sponsor's resubmission of clinical item #5 is presented in two parts. The first portion focuses on the proposed labeling issue of using a second patch after 2 hours. The second part of the review addresses the number of maximum recommended patches that can be used in one month.

Use of a second patch after 2 hours

The issue regarding use of a second patch had been discussed and agreement reached between the FDA and NuPathe at a pre-NDA meeting held on November 24, 2009. The following are the meeting minutes regarding the use of a second patch (item 3 of the meeting):

> **Sponsor's Question**
> The NP10l-007 efficacy and safety study permitted-the-use-of only one NP 101 patch during the study. However, in the long term safety studies NP 101-008 and NP 101-009, patients who experience a return of the headache or a partial response are permitted to apply one additional NP101 patch starting two hours following application of the first NP101 patch. This is a regimen reflected in the label for sumatriptan (Imitrex) 25, 50, and 100 mg oral tablets. Sumatriptan 6 mg subcutaneous injection is also recommended for up to two doses per 24 hours with the second dose to be administered as soon as one hour post-initial application. Sumatriptan 20 mg nasal spray is also recommended up to two doses per 24 hours with a rescue dose two hours after the first dose. Given that pharmacokinetic results demonstrate that NP 101 produces sumatriptan plasma concentrations intermediate between two established sumatriptan formulations - oral tablets 100 mg and nasal spray 20 mg, NuPathe is planning to use the same labeling as the available sumatriptan formulations. The maximum recommended dose will be two NP 101 patches in any 24 hour period with a second patch administration separated by at least two hours from the first application.

Based on the above labeling information for approved sumatriptan formulations and the outcome of our safety studies (NI 101-008 and NP 101-009), we plan to pursue labeling permitting the use in this way of up to two NP 101 patches during any 24 hour period.

Is this plan acceptable to the FDA?

Preliminary Response by FDA
No. In order to support the use of a second patch of NP101, you need to provide evidence of safety and effectiveness of the second patch, e.g. by re-randomizing patients who failed to respond to a first dose or had a headache recurrence to active treatment or placebo, and evaluating the response at an appropriate time point. We also noted that in your controlled efficacy trial subjects were instructed to place the patch on the upper arm, but in your long-term safety study subjects were allowed to place the patch on either the upper arm or the upper thigh. Please provide a justification for that difference, as it raises labeling issues.

Meeting Discussion
The Sponsor indicated that they do not plan to propose labeling to permit a second dose.

(Source: Memorandum of Meeting Minutes; Pre-NDA meeting held on 24 November 2009 between FDA and NuPathe, Inc.)

There were no further discussions held between the FDA and the sponsor regarding the use of a second patch. In the NDA submission, no specific analyses were conducted evaluating the effect of using a rescue patch 2 hours after initial patch use. In the resubmission, the sponsor did not address the meeting of November 24, 2009. The sponsor also did not provide any data showing the efficacy of a second patch 2 hours after initial patch activation.

In the submitted label, however, the sponsor proposed the following statement regarding the use of a second patch:

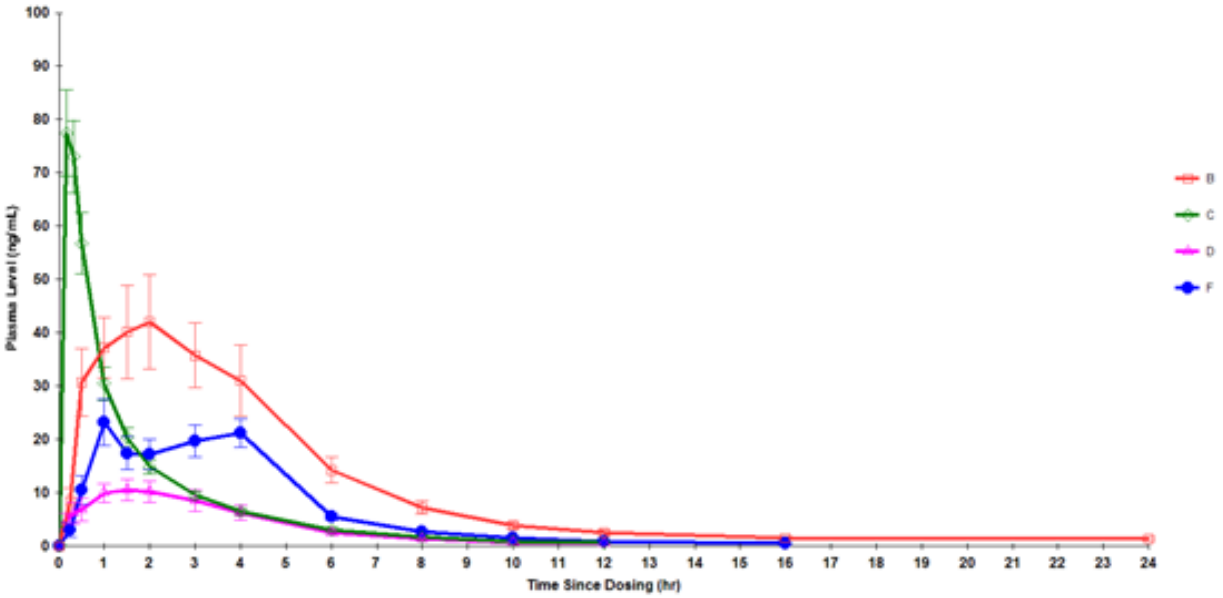
"One ZECUITY patch is the maximum single recommended adult dose. (b) (4)

(b) (4)

In the resubmission, the sponsor summarized skin examination scores by time point following rescue patch application (second patch applied 2 to 24 hours after initial patch) for subjects who applied at least one rescue patch (n=200) in the long term safety studies. These scores were compared with skin scores of the same subjects after their first patch application. There were no major differences in skin examination scores in the two groups (data not shown).

Subsequent to the resubmission, the sponsor provided information justifying the application of a second patch as early as 2 hours after initial patch application. In their correspondence to the FDA (dated 12/28/12), the sponsor demonstrated that the systemic exposure to sumatriptan with Zecuity is substantially less than with 100 mg Imitrex tablet, the reference agent (Table 8).

Table 8 Mean Sumatriptan Plasma Concentration Over Time



Treatment B (n=23): 100 mg sumatriptan oral tablet
Treatment C (n=23): 6 mg sumatriptan subcutaneous injection
Treatment D (n=23): 20 mg sumatriptan nasal spray
Treatment F (n=17): ZECUITY

(Source: Sponsor's correspondence to FDA submitted on 12/28/12)

The sponsor added that it therefore follows that the systemic exposure to sumatriptan after dosing with two Zecuity patches will be less than dosing with two 100 Imitrex tablets, when the dosing interval for each is 2 hours.

Moreover, the sponsor pointed out that plasma sumatriptan concentration following 100 mg Imitrex tablet remains at therapeutic levels up to 6 hours after dosing. Dosing of a second Imitrex tablet is therefore occurring in the setting of continued absorption of sumatriptan from the first dose. This is similar to what occurs when re-dosing with Zecuity at 2 hours.

Safety issues related to re-dosing with the patch at 2 hours were also addressed in the submission dated 12/28/12 from the sponsor. The sponsor reported that adverse events reported by subjects applying a second path within 2 to 4 hours

of a previous patch were comparable to overall study results. Of the 106 subjects who applied a second patch, a total of 33 adverse events were reported by 14 subjects. Adverse events for these subjects were as follows: application site discomfort 10 (30%), pain 6 (18%), pruritus 13 (39%), bruising 2 (6%), discoloration 1 (3%), and hyperesthesia 1 (3%). All adverse events resolved and there were no triptan adverse events reported in the 106 subjects who applied a second rescue patch application.

In conclusion, labeling should state the maximum recommended dose to be only one transdermal patch and that no more than two patches should be used in any 24 hour period. The second patch should not be applied sooner than 2 hours after activation of the first patch.

Maximum patch applications in a month

The sponsor has proposed the following statement regarding maximum patch applications in the label:

(b) (4)

Similar to the lack of sufficient information regarding the use of a second patch 2 hours after the initial patch, no specific analyses were conducted in the NDA justifying the use of (b) (4) patch applications in one month.

Exposure data assessing the safety profile of the patch submitted in the NDA evaluated subjects that used at least 2 patches a month for 6 months and at least 2 patches a month for 12 months. The average patch use in 6 months for 6-month completers was 2.6 patches. The 12-month completers used an average of 2.4 patches per month (Table 9).

Table 9 Summary of Patch Usage in Long Term Safety Studies

Parameter	NP101* (N=662)	6 Month Completers** (N=340)	12 Month Completers*** (N=259)
Average Patches per Month			
n	660	340	259
Mean	1.93	2.62	2.41
SD	1.141	1.235	1.110
Median	1.67	2.33	2.18
Min, max	0.1, 6.0	1.0, 7.0	0.8, 6.0
Average Patches per Month			
0 to 1	182	13	17
1.1 to 1.5	109	54	46
1.6 to 1.9	87	47	47
2.0 to 2.5	124	86	50
2.6 to 3.0	61	47	34
> 3.0	97	93	65
Patch Usage			
Patch used to treat Migraine	8649	7537	6656
Rescue Patch	516	440	369
Rescue Med	521	415	340
Rescue Patch and Rescue Med	58	40	27

* Includes all exposure records, ** Includes exposure records from Day 1 to Day 195, *** Includes exposure records from Day 1 to Day 390.

(Source: Sponsor's resubmission; Integrated Summary of Safety, Section 5.3.5.3, Table 14.4.1.10)

In the resubmission, the sponsor provided data on skin examination scores and treatment emergent adverse events by subgroups of subjects based on number of patches used per month. Subjects were separated into the following groups: ≤2 patches per month (n=409), >2 patches per month (n=201), ≤4 patches per month (n=569) and >4 patches per month (n=41). Of note is the small number of subjects in the subgroup that applied >4 patches per month.

Review of skin examination scores by time point for subjects that used ≤2 patches, >2 patches, ≤4 patches, and >4 patches per month revealed relatively similar scores for all the groups. Data showing skin examination scores at 4 hours and at 24 hours after patch activation for the 4 groups is presented below.

Table 10 Summary of Subject Skin Examination Scores at 4 and 24 Hours for Subjects Applying ≤2, >2, ≤4, or >4 Patches per Month

Distribution at 4 Hours	**≤2 patches/month** N=409	**>2 patches/month** N=201	**≤4 patches/month** N=569	**>4 patches/month** N=41
Skin Score	N (%)	N (%)	N (%)	N (%)
No redness (0)	778 (25.5)	943 (16.1)	1440 (20.2)	281 (15.9)
Minimal redness (1)	803 (26.3)	1918 (32.8)	2112 (29.7)	609 (34.4)
Moderate redness (2)	1270 (41.7)	2770 (47.4)	3191 (44.8)	849 (47.9)
Intense redness (3)	184 (6.0)	203 (3.5)	354 (5.0)	33 (1.9)
Intense w/ blisters (4)	13 (0.4)	10 (0.2)	23 (0.3)	0
Missing	8	0	8	0
Total	3048	5844	7120	1772

Distribution at 24 Hrs	**≤2 patches/month** N=409	**>2 patches/month** N=201	**≤4 patches/month** N=569	**>4 patches/month** N=41
Skin Score	N (%)	N (%)	N (%)	N (%)
No redness (0)	1800 (59.2)	3457 (59.8)	4251 (60.2)	1006 (57.0)
Minimal redness (1)	594 (19.5)	1100 (19.0)	1331 (18.9)	363 (20.6)
Moderate redness (2)	581 (19.1)	1162 (20.1)	1352 (19.2)	391 (22.2)
Intense redness (3)	55 (1.8)	61 (1.1)	111 (1.6)	5 (0.3)
Intense w/ blisters (4)	11 (0.4)	3 (0.1)	14 (0.2)	0
Missing	10	0	10	0
Total	3041	5783	7059	1765

Notes: ACD subjects have been excluded from analyses. “Missing” represents the number of subjects who did not provide at least 1 skin score at that particular time point. Missing is not included in the denominator. The denominator is the total number of patients with a score at a particular time point.

(Source: Adapted from Sponsor’s resubmission; Integrated Summary of Safety, Section 5.3.5.3, Tables 14.12.1.1b through 14.12.1.1e)

It is interesting to note from Table 10 that almost half of the subjects in all groups had moderate redness (skin score of "2") 4 hours after patch activation and that the moderate erythema persisted in approximately 20% of these subjects 24 hours after patch activation.

Treatment emergent adverse events by subgroups of subjects based on number of patches used per month (≤2 patches, >2 patches, ≤4 patches, and >4 patches) were also presented in the resubmission. Review of the data showed no appreciable difference in adverse events, including hypersensitivity reactions, in the subgroups (data not shown).

Overall, the resubmission did not provide sufficient justification for the safety of

(b) (4)

CLINICAL ITEM #6

You have not provided sufficient information to allow us to determine the minimal amount to time necessary to safely reapply the product at the same site. Your NDA provides evidence that the product has a significant irritation potential and is sensitizing. Therefore, it is particularly important to establish how soon the product can be reapplied at the same site. Your proposed language in labeling stating that "ZECUITY should not be applied to a previous application site until the site remains erythema free for 72 hours" is not supported by empirical evidence that it is safe to do so. Your application must include adequate and sufficient safety information to establish the minimum time between treatments that are necessary to safely reapply the product, particularly in patients who exhibited local signs of irritation with the previous treatment.

Review of Resubmission

Subjects in the long term safety studies were required to complete a skin self-examination evaluation at 4, 6, 12, and 24 hours after patch activation as well as daily until resolution of skin erythema. A five-point skin assessment scale was used: 0 = no redness; 1 = minimal skin redness; 2 = moderate skin redness with sharp borders; 3 = intense skin redness with or without swelling; and 4 = intense skin redness with blisters or broken skin.

Subjects were permitted to apply a new patch to the same site as a previous patch application site if the site had a skin examination score of "0" after 72 hours. In the resubmission, the sponsor summarized skin examination scores by time point for subjects who applied an initial patch to arm or thigh site and patch applied to the same arm or thigh site 72 to 144 hours after skin score of "0". Similar summaries were provided using a narrower time window, 72 to 96 hours. The sponsor also reported on subjects who had a skin examination score of 3 or 4 following the initial application who then reapplied the patch to the same site following a 72 to 144 hour period of "0" score.

Skin examination scores were presented by time points starting at 4 hours (within 10 minutes after patch activation) and continuing 8 to 9 days after patch removal. The sponsor reported that of the subjects that reapplied the patch to the same site on the arm or thigh within 72 to 144 hours after skin score of "0", the effect on the skin for reapplication of the patch to same site appeared to be the same as the effect on the skin following the first patch used at the same site.

In reviewing the data, I chose to focus attention on an arbitrary skin assessment time point of 24 hours after patch removal. I summarized skin assessment scores at 24 hours after patch removal for subjects who applied an initial patch to arm or thigh site and patch applied to the same site arm or thigh site 72 to 144 hours after skin score of "0". Data are presented in the table below.

Table 11 Summary of Subject Skin Examination Scores at 24 Hours Post Patch Removal for Subject's Having at Least One Record Applied Within 72 to 144 Hours of Last Skin Assessment Score of 0 (Arm or Thigh, First Patch) and for Same Site (Arm or Thigh, Repeat Patch) in Safety Population

24 Hour Distribution	Arm, first patch	Arm, repeat patch	Thigh, first patch	Thigh, repeat patch
	N=124	N=345	N=111	N=318
Skin Score	N (%)	N (%)	N (%)	N (%)
No redness (0)	62 (50.0)	223 (64.6)	56 (50.5)	226 (71.1)
Minimal redness (1)	37 (29.8)	52 (15.1)	25 (22.5)	39 (12.3)
Moderate redness (2)	24 (19.4)	67 (19.4)	25 (22.5)	51 (16.0)
Intense redness (3)	1 (0.8)	2 (0.6)	5 (4.5)	2 (0.6)
Intense w/ blisters (4)	0	1 (0.3)	0	0
Missing	488	478	501	496

Notes: ACD subjects have been excluded from analyses. "Missing" represents the number of subjects who did not provide at least 1 skin score at the 24 hour time point. Missing is not included in the denominator. The denominator is the total number of patients with a score at the 24 hour distribution time point.

(Source: Adapted from Sponsor's resubmission; Integrated Summary of Safety, Section 5.3.5.3, Tables 14.12.1.1f, through 14.12.1.1i)

As stated above, the sponsor concludes that "the effect on the skin looking at the 72-144 hour time window for reapplication to the same site on the arm or the thigh appears to be the same as the effect on the skin following the first patch used at the same site". While this maybe true, a more noteworthy assessment not discussed by the sponsor are the percentages of subjects reporting erythema 24 hours after patch removal (either with first patch or repeat patch use).

On average, half of the subjects with first patch use reported skin scores ranging from minimal redness to intense redness with blisters or open skin (skin score of 1 to 4), 24 hours after patch removal. Over a third of subjects that applied another patch to same site within 72 to 144 hours after skin score of "0" reported erythema score of ≥1 twenty-four hours post patch removal.

The sponsor provided similar analyses to the 72 to 144 hour time window for reapplication of the patch to the same skin site on the effect on the skin using a narrower window of 72 to 96 hours. In reviewing the data, I again chose to focus attention on an arbitrary skin assessment time point of 24 hours after patch removal. Summary of skin assessment scores at 24 hours for subjects who applied a second patch to the same site 72 to 96 hours following a skin irritation score of "0" and for the first patch applied to the same site (Table 12).

Table 12 Summary of Subject Skin Examination Scores 24 Hours Post Patch Removal for Subject's Having at Least One Record Applied Within 72 to 96 Hours of Last Skin Assessment Score of 0 (Arm or Thigh, First Patch) and for Same Site (Arm or Thigh, Repeat Patch) in Safety Population

24 Hour Distribution	Arm, first patch N=60	Arm, repeat patch N=111	Thigh, first patch N=64	Thigh, repeat patch N=104
Skin Score	N (%)	N (%)	N (%)	N (%)
No redness (0)	32 (53.3)	69 (62.2)	34 (53.1)	72 (69.2)
Minimal redness (1)	14 (23.3)	15 (13.5)	12 (18.8)	14 (13.5)
Moderate redness (2)	14 (23.3)	26 (23.4)	15 (23.4)	16 (15.4)
Intense redness (3)	0	1 (0.9)	3 (4.7)	2 (1.9)
Intense w/ blisters (4)	0	0	0	0
Missing	552	548	548	545

Notes: ACD subjects have been excluded from analyses. "Missing" represents the number of subjects who did not provide at least 1 skin score at the 24 hour time point. Missing is not included in the denominator. The denominator is the total number of patients with a score at the 24 hour distribution time point.

(Source: Adapted from Sponsor's resubmission; Clinical Overview, Section 2.7.4.8.1.2, Tables 14.12.1.1j, k, l and m)

The sponsor reported that skin examination results were the same for subjects waiting 72 to 96 hours before reusing a patch application site after it had been erythema-free as those waiting 72 to 144 hours. It was also reported by the sponsor that reapplying the patch to the same site 72-96 hours after a skin irritation score of "0" appeared to be the same as the effect on the skin following the first patch used at the same site.

Again, what was not discussed by the sponsor was the relatively high number of subjects that reported a skin irritation score greater than "0" after patch removal. Over 50% of subjects reported skin examination scores of ≥1 twenty-four hours after first patch application. Approximately, a third of subjects that applied another patch to same site within 72 to 96 hours after skin score of "0" reported erythema score of ≥1 twenty-four hours post patch removal.

The sponsor also reported on subjects who had a skin examination score of 3 or 4 following the initial patch application who then reapplied the patch to the same site following a 72 to 144 hour period of "0" score. As in the prior analyses, I concentrated my attention on an arbitrary skin assessment time point of 24 hours after patch removal. Skin assessment scores at 24 hours for subjects who had a skin examination score of 3 or 4 after the initial patch application and who then applied a second patch to the same site 72 to 144 hours later are summarized in Table 13.

Table 13 Summary of Subject Skin Examination Scores 24 Hours Post Patch Removal for Subject's having at Least One Record Applied Within 72 to 144 Hours of Last Skin Assessment Score of 0 at Same Site with Score ≥3 (Arm or Thigh, First Patch) and for Same Site (Arm or Thigh, Repeat Patch) in Safety Population

24 Hour Distribution	Arm, first patch N=9	Arm, repeat patch N=11	Thigh, first patch N=8	Thigh, repeat patch N=10
Skin Score	N (%)	N (%)	N (%)	N (%)
No redness (0)	5 (55.6)	6 (54.5)	3 (37.5)	5 (50.0)
Minimal redness (1)	1(11.1)	5 (45.5)	1 (12.5)	2 (20.0)
Moderate redness (2)	2 (22.2)	0	2 (25.0)	2 (20.0)
Intense redness (3)	1 (11.1)	0	2 (25.0)	1 (10.0)
Intense w/ blisters (4)	0	0	0	0
Missing	603	603	604	604

Notes: ACD subjects have been excluded from analyses. "Missing" represents the number of subjects who did not provide at least 1 skin score at the 24 hour time point. Missing is not included in the denominator. The denominator is the total number of patients with a score at the 24 hour distribution time point.

(Source: Adapted from Sponsor's resubmission; Clinical Overview, Section 2.7.4.8.1.2, Tables 14.12.1.1p, q, r, and s)

It was concluded by the sponsor that there was "no evidence for increased skin irritation if a subject who experienced a skin examination score of 3 or 4 reapplied a patch to the same site following a 72-hour period of "0" score". While the number of subjects reviewed was small, what was not discussed by the sponsor was the number of subjects that reported a skin irritation score greater than "0" after patch removal. Approximately half of the subjects in each group had erythema at patch site 24 hours out.

The sponsor evaluated data with an erythema-free time period that extended well beyond the 72 hours that is stated in labeling. The data incorporated subjects waiting up to 96 or 144 hours prior to patch reapplication. It can be postulated that subjects who waited up to 96 or 144 hours prior to applying another patch to the same site allowed for more healing time than those who waited 72 hours. Therefore, the labeling claim that the patch "should not be applied to a previous application site until the site remains erythema free for 72 hours" was not substantiated.

Similar to Clinical Item #5, the FDA requested the further information regarding this matter from the sponsor. In a correspondence dated 1/2/13, the FDA asked the following:

> ***FDA Comment: To justify your proposed labeling that "ZECUITY should not be applied to a previous application site until the site remains erythema free for at least 3 days (not 4 days)", you submitted analyses by time point for subjects who applied a second patch to the same site 72 to 144 hours following a skin irritation***

score of "0", and a parallel set of analyses, for both arm and thigh, were performed with the narrower time window of patches applied to the same site 72 to 96 hours after skin score of "0".

As discussed in our response to your proposed labeling, FDA considers that your analyses only support application to a previous site after 4 days, as the time frame 72 to 96 hours is inclusive of a 4-day interval. In order to support application to a previous site after 3 days, please submit analyses similar to those describe above (i.e., similar to those presented in table 14.12.1.f to 14.12.1.1.m), but limited to patients who applied the second system 72 hours (+/- 6 hours) after the first system.

The sponsor responded on 1/7/13 in an Information Amendment. The sponsor provided data of skin examination scores by time point for subjects who applied a second patch to the same site 66 to 78 hours after a skin irritation score of "0". The following analyses were conducted: initial patch applied to arm site and patch applied to same site within 66 to 78 hours after skin score of "0"; initial patch applied to thigh site and patch applied to same site within 66 to 78 hours after skin score of "0" (Table 14).

Table 14 Summary of Subject Skin Examination Scores 24 Hours Post Patch Removal for Subject's Having at Least One Record Applied Within 66 to 78 Hours of Last Skin Assessment Score of 0 (Arm or Thigh, First Patch) and for Same Site (Arm or Thigh, Repeat Patch) in Safety Population

24 Hour Distribution	Arm, first patch N=41	Arm, repeat patch N=67	Thigh, first patch N=46	Thigh, repeat patch N=65
Skin Score	N (%)	N (%)	N (%)	N (%)
No redness (0)	19 (46.3)	41 (61.2)	23 (50.0)	40 (61.5)
Minimal redness (1)	8 (19.5)	9 (13.4)	11 (23.9)	12 (18.5)
Moderate redness (2)	14 (34.1)	16 (23.9)	10 (21.7)	12 (18.5)
Intense redness (3)	0	1 (1.5)	2 (4.3)	1 (1.5)
Intense w/ blisters (4)	0	0	0	0
Missing	571	566	566	563

Notes: ACD subjects have been excluded from analyses. "Missing" represents the number of subjects who did not provide at least 1 skin score at the 24 hour time point. Missing is not included in the denominator. The denominator is the total number of patients with a score at the 24 hour distribution time point.

(Source: Adapted from Sponsor's Information Amendment of 1/7/13, Section 5.3.5.3, Tables 14.12.1.1v, w, x, and y)

Results were comparable for skin examination profiles for patch application at 66 to 78 hours following reapplication to the same site on the arm or thigh as the effect on the skin after the initial patch applied to the same application site. Skin examination results were also similar for subjects waiting 66 to 78 hours before reusing a patch application site after it had been erythema-free as those waiting 72 to 144 hours or those waiting 72 to 96 hours.

In conclusion, with the additional analyses, the sponsor has adequately demonstrated that it is safe to re-use the same patch application site after it has been free of erythema for at least 72 hours (3 days).

APPEARS THIS WAY ON ORIGINAL

CLINICAL ITEM #7

There was a high rate of discontinuation in long-term safety studies (55%). The most common reason for discontinuation was "withdrawal of consent" (20% of patients across treatment groups). The reason for the "withdrawal of consent" was not described in your database. As adverse events often lead to patients withdrawing consent, it is critical to determine whether patients who withdrew consent experienced an adverse reaction before withdrawing from the study. For patients who discontinued because of "withdrawal of consent", provide a description of adverse events occurring in the previous 30 days.

Review of Resubmission

An updated accounting of subjects who discontinued from the long term safety studies (NP101-008 and -009) was provided in the resubmission. For study NP101-008, the sponsor reported that discontinuations due to withdrawal of consent were investigated to confirm the reason for discontinuation. These queries were conducted prior to final database lock and confirmed results were included in the original NDA submission. Study NP101-009, however, was ongoing at the time of the original submission. Additional follow-up was conducted prior to final database lock for subjects who discontinued due to withdrawal of consent. This resulted in a change in 10 cases from withdrawal of consent to discontinuation due to an adverse event.

The sponsor's table below provides a summary comparison of the disposition of subjects in the original submission and the updated resubmission which includes the final data for study NP101-009. There was an increase in the total number of subjects who discontinued from the long term safety studies in the resubmitted report. Overall, there was a very high rate of discontinuation. As documented in the final updated data (resubmission), almost 60% of subjects discontinued participation in the long term safety studies (390/711).

Table 15 Comparison of Subject Disposition (Studies NP101-008 and NP101-009) in the Original NDA and in the Resubmission

	Number (%) of Treated Subjects	
	Original NDA[a]	Resubmission[b]
Total Enrolled	711[c]	711[c]
Not treated	49[c]	49[c]
Safety Population	662 (100)	662 (100)
6-month completer	319 (48.2)	340 (51.4)
12-month completer	59 (8.9)	259 (39.1)
Completed study	73 (11.0)	272 (41.1)
Discontinued study	363 (54.8)	390 (58.9)
Lost to follow-up	39 (5.9)	49 (7.4)
Adverse event	85 (12.8)	99 (15.0)
Subject withdrew consent	129 (19.5)	127 (19.2)
Non-compliance with study drug	57 (8.6)	59 (8.9)
Other	53 (8.0)	56 (8.5)

[a] Study visits completed through 06 September 2010 (Study NP101-009).
[b] Last subject, last visit of 09 May 2011 (Study NP101-009).
[c] One subject enrolled but not treated in Study NP101-008 and enrolled and treated in Study NP101-009 is only counted once in the combined total.

(Source: Sponsor's resubmission; Clinical Summary, Section 2.7.3.4.2.1.1, Table 11)

Withdrawal of consent and adverse events constituted the most common reasons for discontinuations. In the final analysis, 19% of all subjects (127/711) withdrew consent from the study. Another 15% of subjects (99/711) in the study discontinued due to adverse events.

Reasons for withdrawal of consent were not adequately provided in the original submission. In the Clinical Response letter, the sponsor was asked to submit descriptions of adverse events occurring within 30 days prior to withdrawal.

The sponsor reported that of the 127 subjects that withdrew consent in the updated data, 26 subjects (21%, 26/711) experienced an adverse event within 30 days prior to withdrawal from the study. The 26 subjects reported a total of 45 adverse events. The majority of adverse events (73%) were due to patch application site conditions (33 out of 45 events). Please refer to Table 16 for a distribution of these adverse events.

Table 16 Adverse Events Occurring within 30 Days Prior to Discontinuation in Subjects that Discontinued due to Withdrawal of Consent (Studies NP101-008 and NP101-009)

System Organ Class MedDRA Preferred Term	Number (%) of Subjects (N=127)
Subjects with at least one TEAE within 30 days prior to discontinuation	26 (20.5)
General disorders and administration site conditions	
Application site exfoliation	1 (0.8)
Application site hyperaesthesia	1 (0.8)
Application site pain	16 (12.6)
Application site papules	1 (0.8)
Application paraesthesia	3 (2.4)
Application site pruritus	9 (7.1)
Application site reaction (burning sensation, not painful)	2 (1.6)
Other events[a]	
Asthma	1 (0.8)
Blood pressure	2 (1.6)
Headache	1 (0.8)
Influenza	1 (0.8)
Lymph node pain	1 (0.8)
Muscle spasms	1 (0.8)
Pelvic pain	1 (0.8)
Sinus headache	1 (0.8)
Vertigo	3 (2.4)

[a] All other events were not related to NP101.

(Source: Sponsor's resubmission; Clinical Summary, Section 2.7.4.2.1.4.3, Table 25)

By far, the most common adverse event reported within 30 days in subjects that discontinued due to withdrawal of consent was pain from patch application site. Of the 33 adverse events related to the patch, almost half (16 of 33 adverse events; 49%) were due to application site pain.

The sponsor also reported that of the 33 adverse events related to the patch, 17 events (52%) resolved the same day. The mean time to resolution of the remaining 16 adverse events was 6 days. Overall, 20 patch-related adverse events were reported as mild and 13 were reported as moderate.

In summary, there was a very high rate of discontinuation in the long term safety studies. Over half of all subjects (59%) discontinued participation. Withdrawal of consent and adverse events were the major reasons for discontinuation. For those that withdrew consent, 20% reported having an adverse event within 30 days of withdrawal. Adverse events leading to discontinuation were predominantly due to patch application site conditions.

CLINICAL ITEM #8

Your 6-month safety database includes a lower number of patients who have treated an average of at least 2 migraine attacks per month than discussed with you during the development program. Specifically, our typical requirement for acute migraine products is for data on at least 300 subjects who treated an average of at least 2 migraine attacks per month for six months, and 100 subjects who treated an average of at least two migraine attacks for one year. At the pre-NDA meeting, the division agreed to your proposal for a database of at least 300 patients treated with an average of three patches per month for six months, and 50 patients treated with an average of three patches per month for 12 months. We acknowledge that your database includes a sufficient number of patients exposed for 12 months. However, your 6-month database provides data on only 165 patients who treated an average of greater than 2 attacks per month, and 74 patients who treated an average of greater than 3 attacks per month*. Assuming you adequately address the clinical safety issues described above (under clinical comments 1-7), additional 6-month long-term safety data may be required.

(*Because of the way your data presentation was structured, we could derive the number of patients who treated an average of greater than 2 attacks per month, but not the number of patients who treated an average of at least 2 attacks per month.)

Review of Resubmission

In the resubmission, the sponsor recalculated the average number of transdermal patches used per month based on individual subject average rather than the overall subject average employed in the original submission. The sponsor also determined the average patch use for 6-month completers by restricting the group to 6 months of exposure. In the original NDA submission, the average patch use for 6-month completers included data for some subjects who used patches for longer than 6 months. The sponsor analyzed final data from both completed long term studies (NP101-008 and NP101-009).

Using the criterion of an individual subject average of at least 2 patches applied per month in the combined long-term studies, 226 subjects met the criterion for 6 months and 149 subjects met it for 12 months. The average patch use in 6 months for 6-month completers was 2.6 patches. The 12-month completers used an average of 2.4 patches per month. Please refer to Table 17 for details.

Table 17 Summary of Patch Usage in Long Term Safety Trials (NP101-008 and NP101-009)

Parameter	NP101* (N=662)	6 Month Completers** (N=340)	12 Month Completers*** (N=259)
Average Patches per Month			
n	660	340	259
Mean	1.93	2.62	2.41
SD	1.141	1.235	1.110
Median	1.67	2.33	2.18
Min, max	0.1, 6.0	1.0, 7.0	0.8, 6.0
Average Patches per Month			
0 to 1	182	13	17
1.1 to 1.5	109	54	46
1.6 to 1.9	87	47	47
2.0 to 2.5	124	86	50
2.6 to 3.0	61	47	34
> 3.0	97	93	65
Patch Usage			
Patch used to treat Migraine	8649	7537	6656
Rescue Patch	516	440	369
Rescue Med	521	415	340
Rescue Patch and Rescue Med	58	40	27

* Includes all exposure records, ** Includes exposure records from Day 1 to Day 195, *** Includes exposure records from Day 1 to Day 390.

(Source: Sponsor's resubmission; Integrated Summary of Safety, Section 5.3.5.3, Table 14.4.1.10)

At the End of Review meeting held with the sponsor on November 9, 2011, the sponsor specifically asked the Agency whether the updated exposure data in the long-term safety program was adequate to define the safety profile of NP101. The Agency reviewed the data and found the overall updated exposure of the long term safety program to be adequate. (Please refer to the response and meeting discussion to question #15 of the meeting minutes held with the sponsor on November 9, 2011 for details).

In conclusion, 226 subjects used an average of 2.6 patches per month for 6 months and 149 subjects used an average of 2.3 patches a month for 12 months. While the average numbers of monthly exposures in the updated data for the 6-month completer group is still less than the typical requirement of at least 300 subjects, the combined 6-month and 12-month total exposures of 375 subjects, is deemed sufficient to adequately assess the safety profile of NP101.

CLINICAL ITEM #9

While we acknowledge that pivotal efficacy Study NP101-007 established the efficacy of your product in the overall migraine population, we note there was essentially no treatment benefit for the 2-hour pain-free rate in non-White patients* (active patch 12.5%; placebo patch 11.4%). In addition, clinical pharmacology studies suggest that sumatriptan exposure (Cmax and AUC) may be lower in non-White patients than in White patients, which gives credence to a possible lack of efficacy in non-White patients. Please address these findings, and provide evidence supporting the efficacy of the product in non-White patients.

***(In the analyses of race group presented in the efficacy study (NP101-007), the non-white population included all subjects who reported their race as Black, Asian, American Indian/Alaska Native, or Pacific Islander/Native Hawaiian).**

Review of Resubmission

In the review of the original submission, the efficacy of NP101 patch in non-white subjects came into question as subgroup analyses and pharmacokinetic studies indicated that the product was no better than placebo in non-white subjects.

In the resubmission, the sponsor emphasized that the efficacy study was not powered to definitively determine non-efficacy in the non-white population. Pertinent issues discussed in the resubmission regarding efficacy of NP101 in non-white subjects focused on 2 major points:

- Additional analyses were provided comparing differences in the proportion of subjects with reduction in headache pain for NP101 versus placebo within each subpopulation (white and non-white subjects) and between white and non-white subjects within each treatment group (NP101 and placebo) in the efficacy study.
- Pooled pharmacokinetic data from 8 Phase 1 studies were analyzed assessing the effect of race on the pharmacokinetics of NP101.

Reduction of headache pain in whites and non-white subjects

The sponsor provided data on change in headache pain at 2 hours after patch application by race group (Table 18). Headache pain was rated on a 4-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe).

When assessing for efficacy in reduction of headache pain, a 2-point or greater improvement (on a 4-point headache pain scale) is used. For example, a 2-point improvement in headache is a decrease from severe to mild headache (from a score of 3 down to 1 on the headache scale) or from moderate headache to no pain (from 2 to 0). A 3-point improvement is a reduction from severe headache to no pain (from a score of 3 down to 0 on the headache scale).

Table 18 Summary of Pain Intensity Shift 2 Hours after Patch Application by Race Group

Category	Pain Intensity Pre-Treatment - Post Treatment	NP101 Non-White (N=40)	NP101 White (N=186)	Placebo Non-White (N=44)	Placebo White (N=184)
Improved 3 Points	Total	1 (2.50%)	2 (1.08%)	1 (2.27%)	2 (1.09%)
	Severe - No Pain	1 (2.50%)	2 (1.08%)	1 (2.27%)	2 (1.09%)
Improved 2 Points	Total	6 (15.00%)	43 (23.12%)	4 (9.09%)	18 (9.78%)
	Moderate - No Pain	4 (10.00%)	33 (17.74%)	4 (9.09%)	14 (7.61%)
	Severe - Mild	2 (5.00%)	10 (5.38%)	0	4 (2.17%)
Improved 1 Points	Total	18 (45.00%)	71 (38.17%)	16 (36.36%)	46 (25.00%)
	Moderate - Mild	9 (22.50%)	57 (30.65%)	11 (25.00%)	30 (16.30%)
	Severe - Moderate	9 (22.50%)	14 (7.53%)	5 (11.36%)	16 (8.70%)
No Change	Total	12 (30.00%)	56 (30.11%)	19 (43.18%)	96 (52.17%)
	Moderate - Moderate	11 (27.50%)	47 (25.27%)	16 (36.36%)	70 (38.04%)
	Severe - Severe	1 (2.50%)	9 (4.84%)	3 (6.82%)	26 (14.13%)
Worsening	Total	3 (7.50%)	11 (5.91%)	4 (9.09%)	21 (11.41%)
	Moderate - Severe	3 (7.50%)	11 (5.91%)	4 (9.09%)	21 (11.41%)
Missing/Incomplete Data	Total	0	3 (1.61%)	0	1 (0.54%)
	Missing - Mild	0	1 (0.54%)	0	0
	Missing - Moderate	0	1 (0.54%)	0	1 (0.54%)
	No Pain - Moderate	0	1 (0.54%)	0	0
Fisher's Exact 2-sided Test [2]	NP101 vs Placebo | NON-WHITE	0.1946	0	0	0
	NP101 vs Placebo | WHITE	<.0001	0	0	0
	White vs NonWhite | NP101	1.0000	0	0	0
	White vs NonWhite | Placebo	0.1694	0	0	0

[1] Pain intensity was to be collected 2 hours after patch application. A subject applied one patch in study.
[2] P-value for testing difference in proportion of patches with/without pain reduction. Reduction = Yes if pain intensity after treatment was reduced by 1, 2, or 3 points; Reduction = No if pain intensity after treatment was same or worsening.

(Source: Sponsor's resubmission; Summary of Clinical Safety, Section 2.7.3, Appendix 6.2, Table 18)

Among subjects who received NP101, white subjects had a greater improvement in headache pain than non-white subjects at 2 hours post patch application (using a 2-point or greater improvement of migraine pain on a 4-point scale). As calculated from Table 18, 24.2% (45/186) of white subjects had a greater reduction in headache versus 17.5% (7/40) of non-white subjects. Among subjects who received placebo, there was no appreciable difference between white and non-white subjects in percent of subjects with reduction in pain (10.9% versus 11.4%, respectively).

Among white subjects, there was a clear difference between treatment groups in the percent of subjects with a reduction in pain at 2 hours (24.2% in the NP101 group versus 10.9% in the placebo group). Among non-white subjects, more NP101 treated subjects had pain reduction than placebo subjects (17.5% versus 11.4%, respectively). See table 19.

Table 19 Improvement from Baseline Headache Pain at 2 Hours after Patch Application for White and Non-White Subgroups in Study NP101-007

	NP101		Placebo	
Change in Pain Score	**Non-white (N=40) N (%)**	**White (N=186) N (%)**	**Non-white (N=40) N (%)**	**White (N=186) N (%)**
Improved[a]	7 (17.5)	45 (24.2)	5 (11.4)	20 (10.9)

[a]At least 2-point improvement from baseline in pain score
(Source: Adapted from sponsor's resubmission; Summary of Clinical Safety, Section 2.7.3, Appendix 6.2, Table 18)

In the resubmission, the sponsor conducted similar analyses as I did above. However, instead of using a 2-point or greater improvement in baseline headache pain score, the sponsor calculated improvement by using a 1-point or greater improvement in headache score. The sponsor's data is presented in the table below.

Table 20 Changes from Baseline in Pain Intensity at 2 Hours after Patch Application for White and Non-white Subgroups in Study NP101-007

	NP101			Placebo		
Change in Pain Score	**Non-white (N=40) n (%)**	**White (N=186) n (%)**	**p-value[a]** (White vs. Non-white)	**Non-white (N=44) n (%)**	**White (N=184) n (%)**	***p*-value[a]** (White vs. Non-white)
Improved[b]	25 (62.5)	116 (62.4)	1.0000	21 (47.7)	66 (35.9)	0.1694
No change	12 (30.0)	56 (30.1)		19 (43.2)	96 (52.2)	
Worsening	3 (7.5)	11 (5.9)		4 (9.1)	21 (11.4)	
Missing/incomplete[c]	0	3 (1.6)		0	1 (0.5)	
p-value[a] (NP101 vs. placebo)	0.1946	<0.0001				

[a] Fisher's Exact 2-sided t-test for difference in proportion of subjects with improvement in pain score vs. no change/worsening in pain score.
[b] At least 1-point improvement from baseline in pain score.
[c] Subjects who reported pain only before or after treatment were counted as missing/incomplete data.
(Source: Sponsor's resubmission; Clinical Summary, Section 2.7.3.4.2.1.1, Table 11)

Using a 1-point or greater headache improvement pain score, the sponsor reported that among white subjects, there was a significant difference between treatment groups (NP101 or placebo) in the percent of subjects with a reduction in headache pain at 2 hours (62.4% of NP101 treated white subjects and 35.9% of placebo treated white subjects; $p<0.0001$). Among non-white subjects, however, the difference in headache pain reduction was not statistically significant (62.5% NP101 and 47.7% placebo; $p<0.1946$). The sponsor noted that while not statistically significant, a treatment effect was still observed among non-white subjects and the sample size for non-whites was too small to achieve statistical significance.

The sponsor applied similar comparisons of white and non-white subjects within each treatment group (NP101 or placebo). Among subjects who received NP101, there was no difference (p=1.0000) between white and non-white subjects with regards to percent of subjects with a reduction of headache pain (62.4% and 62.5%, respectively). Similarly, in the placebo group, there was no significant difference between white and non-white subjects in percent of subjects with a reduction in pain (p=0.1694). The sponsor adds that this provides strong evidence of an NP101 treatment effect in non-white subjects.

As noted previously, the sponsor analyzed data using an improvement of headache pain of 1-point or greater on a 4-point headache rating scale. A 1-point improvement in headache pain does not meet the standards for determination of efficacy for improvement of headache pain. A 1-point improvement in pain is too narrow a treatment difference and does not accurately and consistently gauge tangible improvement of headache pain. A 2-point or greater (out of a 4-point scale) of improvement in headache pain is the typical standard used for determination of migraine efficacy. Thus, the analysis conducted by the sponsor above does not support NP101 treatment effect in non-whites.

Effect of race on pharmacokinetics on NP101

The sponsor evaluated the effect of race on the pharmacokinetics of NP101. Pharmacokinetic parameters of C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-}4}$, and $AUC_{0\text{-inf}}$, were compared for white and non-white subjects. Data from 8 Phase 1 studies were pooled (studies NP101-005, -006, -011, -012, -013, -018, -023, and -024). A total of 195 subjects were enrolled in these studies. Of the 195 subjects, 168 were considered PK evaluable. The 168 subjects consisted of 118 (70.2%) white and 50 (29.8%) non-white subjects. Summary findings of the pooled data are presented in Table 21.

Table 21 Pooled Analyses of Effects of Race on NP101 Pharmacokinetics

	Pooled Study Results[a]			Non-white vs White	
Parameter	Race Group	N	Geometric Mean[b] (95% CI)	Ratio of Geometric Means (95% CI)[b]	*p*-value[c]
C_{max}, ng/mL	Non-white	50	20.88 (19.64, 22.19)	0.92 (0.86, 0.97)	0.0191
	White	118	22.79 (21.90, 23.72)		
$AUC_{0\text{-last}}$, hr*ng/mL	Non-white	50	108.29 (101.37, 115.67)	0.97 (0.91, 1.04)	0.4792
	White	118	111.39 (106.71, 116.28)		
$AUC_{0\text{-}4}$, hr*ng/mL	Non-white	50	57.03 (53.15, 61.19)	0.90 (0.84, 0.96)	0.0108
	White	118	63.65 (60.80, 66.64)		
$AUC_{0\text{-inf}}$, hr*ng/mL	Non-white	50	110.58 (103.57, 118.06)	0.98 (0.91, 1.04)	0.5371
	White	118	113.32 (108.59, 118.25)		

[a] Pooled studies (number of subjects): NP101-005 (17); NP101-006 (2); NP101-011 (18); NP101-012 (27); NP101-013 (30); NP101-018 (30); NP101-023 (32); NP101-024 (12).
[b] All estimates derived from a 1-way ANOVA model of race effect on log transformed parameter value.
[c] Probability >F = *p*-value from F test for race effect on mean exposure in natural log scale.
N=sample size; CI = confidence interval.

(Source: Sponsor's resubmission; Summary of Clinical Efficacy, Section 2.7.3.4.2.1.2, Table 14)

C_{max} is about 8% lower and AUC_{0-4} hours is about 10% lower in non-white compared to white subjects, respectively. These differences are not expected to be clinically significant.

In conclusion, while the sponsor has not fully demonstrated efficacy in non-white subjects at 2 hours after NP101 patch application, the sponsor, however, makes a convincing case regarding the effect of race on the pharmacokinetics of NP101. Review of pooled pharmacokinetic data demonstrates acceptable bioequivalence range of C_{max} and AUC_{0-4} between white and non-white subjects.

APPEARS THIS WAY ON ORIGINAL

4. Labeling Recommendations

Labeling recommendations are pending at the time of this review.

5. Advisory Committee Meeting

No advisory committee was convened for this product.

APPEARS THIS WAY ON ORIGINAL

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

/s/

NUSHIN F TODD
01/14/2013

ERIC P BASTINGS
01/17/2013

MEMORANDUM

DATE: August 28, 2011

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 202-278

SUBJECT: Action Memo for NDA 202-278, for the use of Zecuity (sumatriptan) iontophorectic transdermal system

NDA 202-278, for the use of Zecuity (sumatriptan) iontophorectic transdermal system, was submitted by NuPathe, Inc., on 10/29/2010. This application proposes a new delivery system for sumatriptan, in which a patch delivers sumatriptan through the skin via an electric current. The system has to prepared for use by the patient in a somewhat complex series of steps (this is described in detail by various reviewers). The patient activates the system, which continues to deliver drug (presumably a total of (b) (4) mg) over the next 4 hours, after which the deliver (and the current) ceases. The proposed indication is for the acute treatment of migraine headache. The sponsor has submitted the results of a single randomized controlled trial (Study 007) that purports to establish substantial evidence of effectiveness for the system, as well as long term safety data for the system (Studies 008 and 009), as well as other shorter term Phase 1 studies, in addition to CMC, toxicology, and clinical pharmacology data, as well as additional data related to the device proposed.

The application has been reviewed by Dr. Nushin Todd, medical officer, Dr. Julia Luan, statistician, Dr. Charles Thompson, pharmacology reviewer, Dr. Lois Freed, pharmacology supervisor, Dr. Jagan Parepally, Office of Clinical Pharmacology, Drs. Caroline Strasinger and David Claffey, Office of New Drug Quality Assessment (ONDQA), Dr. Tapash Ghosh, ONDQA, Biopharmaceutics, Geeta Pamidimukkala and Elijah Weisberg, Center for Devices and Radiological Health (CDRH), Dr. Stephen E. Langille, Microbiology, Dr. Snezana Trajkovic, Division of Dermatology Products, Richard Abate, Division of Medication Error Prevention and Analysis, Drs. Charles Bonapace and (b) (4), Office of Scientific Investigations (Division of Bioequivalence), Dr. Antoine El-Hage, Division of Scientific Investigations, and Dr. Eric Bastings, Deputy Director, DNP, Neurology Team Leader, and Cross-Discipline Team Leader (CDTL).

The clinical, pharmacology/toxicology, clinical pharmacology, device, and CMC reviewers all recommend that the application not be approved, and that a Complete Response (CR) letter be issued to the sponsor. I agree.

This application suffers from numerous and significant deficiencies in multiple review areas. These deficiencies have been detailed comprehensively and

extensively in Dr. Bastings's excellent CDTL memo; I will only very briefly recount them here.

Clinical

As noted by numerous reviewers, the results of Study 007 clearly demonstrated the effectiveness of Zecuity in the treatment of an acute migraine headache, as evidenced by a clear showing of drug-placebo differences in the percentage of patients headache-free at 2 hours, as well as in the percentage of patients nausea, photophobia, and phonophobia-free at 2 hours, all of which reach clear statistical significance in favor of the treatment.

Of interest, both Drs. Todd and Bastings note that there seemed to be no difference in outcome between White and non-White patients, despite the clear findings in the population overall. This population made up about 19% of the overall study population.

However, as described clearly by Drs. Todd and Bastings, the use of Zecuity is associated with numerous adverse events of concern; in addition, the sponsor has not submitted adequate information that would permit us to discern whether or not large numbers of patients experienced adverse events of concern.

The adverse events of concern all relate to local skin reactions at the site of application of the system.

Specifically, about 2% of patients on active drug and placebo, each, discontinued treatment during the controlled trial due to adverse events at the site of application. About 55% of the patients discontinued long-term treatment, with about 20% withdrawing due to "withdrawal of consent", not further explained by the sponsor. Of those discontinuing with an explanation provided, about 13% discontinued due to an adverse event, almost all (>90%) of which were related to local skin reactions (including 3.5% for "hypersensitivity" and 3.2% for "pain"). As Dr. Todd also notes, the sponsor's categorization of the many reported local site reactions has made it difficult to assess whether there is overlap in the descriptions, and, therefore, it has been difficult to estimate the true incidence of specific adverse events.

Nonetheless, about 5.4% of patients in Studies 007, 008, and 009 experienced a severe site reaction.

Of particular importance, and although it has been difficult to fully characterize the adverse event profile, at least 3 patients experienced what can be called severe burns at the site of application (an additional 2 patients were reported to have had burns that presumably were not severe), 15 experienced severe pain, and 12 patients experienced hypersensitivity reactions. Dr. Trajkovic of the Dermatology Division has concluded that the system, "has significant irritation

potential and is sensitizing", though it has been difficult to discern if this is due to the drug-device combination, or the device itself, in the absence of drug (of course, the distinction, though of interest, is not particularly relevant in this case).

About 44% of the placebo patients and 50% of the drug-treated patients in the controlled trial experienced at least one adverse event, most of which were related to local site reactions (e.g., pain, pruritus, "reaction", paresthesia, hypersensitivity, dryness, etc.). There was a 2.4% incidence of "bruising", and the appearance of vesicles.

Patients rated themselves according to a 5 point scale when they removed the patch, and at 6, 12, and 24 hours post-removal; the scale is reproduced below:

0- no redness
1- minimal skin redness
2- moderate skin redness with sharp borders
3- intense skin redness with or without swelling
4- intense skin redness with blisters or broken skin

In the controlled trial (Study 007), 88% of patients had a score of at least 1 at 4 hours, and 70% had a score of at least 1 at 24 hours. The mean time to disappearance of redness was about 10 days post application.

In the long-term safety study, about 48% of applications were scored a 2 on the scale at 4 hours, and about 23% were scored a 2 at 24 hours. About 6% were scored at least 3 at 4 hours (0.4% were scored a 4), and about 3% were scored at least a 3 at 24 hours (0.5% were scored a 4).

The sponsor performed a small study (that was to enroll up to 30 subjects) in which subjects were to apply an active patch and a placebo patch to each upper arm each day. Each patch was activated for 4 hours, then left in place for a total of 23 hours. Application of one patch to the same location was to be performed daily for 21 days.

The study was stopped after 10 subjects were enrolled. In this cohort, by Day 5, 4 subjects had scores of 4 on at least one application site. By Day 6, 3 more subjects had a similar score, and by Day 7, all 10 subjects had a score of 4 on at least one site.

CMC

Dr. Strasinger has noted numerous, significant deficiencies in the manufacture of the product, including that there is obvious (to the naked eye) lack of uniformity in the distribution of the drug formulation on the pads, there is obvious lack of containment of the drug in the system (it appears to clearly leak out of the patch),

and there is a lack of evidence that patients can use the product adequately, given the poor manufacturing aspects, and the complexity of preparing the system, which it is necessary for the patient to do before it can be applied. In addition, there are many other deficiencies identified. Numerous of these deficiencies have been communicated to the sponsor by letter (most recently in a letter dated 5/19/11), some of which the sponsor has responded to. Some of the sponsor's responses have been considered adequate, many have not, and most have not yet been reviewed.

Device issues

Many device deficiencies have been identified, including those related to stability, software/firmware, biocompatibility, and required procedural safeguards.

Biopharmaceutics

Dr. Ghosh has identified numerous deficiencies, including deficiencies related to the lack of an adequate in vitro method to evaluate drug permeation as a tool to ensure lot-to-lot variability, as well as other deficiencies.

Clinical Pharmacology

The sponsor has performed sufficient characterization of the pharmacokinetics of the product. In particular, they performed a study comparing the kinetics of the to-be-marketed system with the system actually studied in the clinical trial. Although this study showed equivalence of the two systems, the sponsor's contractor failed to retain samples of the products used, in violation of the relevant regulations, making it impossible to verify the results of the study . For this reason, Dr. Parapelly has recommended that this study be repeated.

Microbiology

Numerous microbiology deficiencies have also been identified, including deficiencies related to inadequate proof of anti-microbial effectiveness, as well as other deficiencies.

Pharmacology/toxicology

Drs. Thompson and Freed note that the sponsor has submitted a 9 month chronic mini-pig toxicology study, which they find to be inadequate due to an inadequate number of animals/group, lack of a control group, and a lack of explanation for why the dosing interval chosen (one patch/week) is adequate. In addition, the system used in the animal study was not identical to that to be marketed.

Further, the sponsor did not perform a dermal carcinogenicity study (as they had been asked to do by the division in previous conversations with them), presumably because they have argued that such a study is not feasible (according to the sponsor, producing a system to be applied in animals that is sufficiently similar to the system proposed for use in humans was not feasible; further, they assert that sumatriptan is not carcinogenic in rats when given orally, and sumatriptan is not mutagenic). Although Drs. Freed and Thompson agree that it would not be possible to produce a system to be used in animals that is similar to that proposed for use in people, they have concluded that the sponsor has not adequately explained why a dermal painting study in rodents cannot be performed, and/or why such a study would not be relevant.

COMMENTS

The sponsor has proposed the use of an iontophoretic patch that delivers sumatriptan through the skin via an electric current. They have performed a single adequate and well-controlled study, which has clearly demonstrated that the device is effective.

However, the use of this system is associated with numerous and frequent local adverse events, including, in some cases, severe burns. Although the incidence of events characterized as severe is relatively few, even these few events raise concerns about the ultimate approvability of such a product for the symptomatic treatment of migraine headaches. Without the sponsor offering an adequate explanation and justification for why such a product should be approved for this indication, I have serious doubts about whether approval would be appropriate.

Further, and of considerable concern in my view, is the observation that numerous patients discontinued the treatment over time, without well-documented reasons for doing so, other than having been labeled as having withdrawn consent. For this reason, I do not believe that the safety profile of this product has been adequately characterized.

Drs. Todd and Bastings have observed that there seems to be no treatment effect in non-white patients, who constitute about 19% of the total study population. Dr. Bastings has further indicated that the product seems to produce lower plasma levels of sumatriptan in non-whites than in whites, suggesting that the difference in clinical response may have kinetic support. Although the difference in response between the groups may be a true finding, in my view, at least at this time, this may simply be an artifact of sub-grouping, and not a “real” finding. Nonetheless, I agree that we should ask the sponsor to address this issue.

Finally, the product is difficult to prepare for use. One could argue that the fact that the clinical trial was positive demonstrates that preparation and use of the system can be used successfully. However, as noted by Dr. Bastings, patients in

the trial received considerable instruction in the use of the product. It seems likely that, under real-world conditions, especially when patients are in the throes of a migraine attack, there will be a considerable number of errors in the preparation and use of the product.

Further, the sponsor proposes that patients not place the patch on the same location sooner than 72 hours after the site is free of erythema. The sponsor has produced no evidence that this maneuver guarantees that significant local adverse events will not occur (this is especially important given the results of the daily patch application study as described above).

Of course, in addition to the critical clinical issues noted, numerous other deficiencies have been identified, including, and especially, the many CMC deficiencies. These must all be adequately addressed before the application can be considered for approval.

For the reasons stated above, then, I will issue the attached Complete Response letter.

Russell Katz, M.D.

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

/s/

RUSSELL G KATZ
08/29/2011

CLINICAL REVIEW

Application Type	NDA, 505(b)(2)
Application Number(s)	202278
Priority or Standard	Standard
Submit Date(s)	10/29/10
Received Date(s)	10/29/10
PDUFA Goal Date	08/29/11
Division / Office	Division of Neurology Products
Reviewer Name(s)	Nushin Todd, M.D., Ph.D.
Review Completion Date	
Established Name	NP101 (sumatriptan) iontophoretic transdermal system
(Proposed) Trade Name	Zelrix
Therapeutic Class	Triptan agonist
Applicant	NuPathe, Inc.
Formulation(s)	Iontophoretic transdermal patch
Dosing Regimen	Single 6.5 mg sumatriptan transdermal patch, electrically dispensed over 4 hours
Indication(s)	Acute migraine
Intended Population(s)	Adult patients with migraine

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend a Complete Response action.

This recommendation is based on the following clinical deficiencies:

- There is significant irritation potential of the product with high incidence of application site conditions (e.g., close to half of all subjects in the safety population had an adverse event at site of patch application; 5% of the application site reactions were severe, including 3 cases of severe skin burns)
- There is inadequate information describing adverse skin reactions (e.g., use of non-specific terms such as “application site reaction” and “application site irritation”, and splitting of preferred terms)
- There is inadequate information on final outcome of severe skin reactions such as third degree burns, hypersensitivity reactions, and discoloration
- There is inadequate information to support efficacy of the product in non-white subjects
- There is inadequate information on reasons for treatment discontinuations and withdrawal of consent
- There is inadequate information regarding minimal time between 2 applications of the patch at the same site
- The number of patch exposures by subjects in the long term safety studies was less than agreed upon with the Agency

In addition to the clinical deficiencies, Chemistry Manufacturing and Controls (CMC) Division has determined the fundamental design of NP101 to be unacceptable. CMC cannot adequately assure identity, strength, quality, purity, potency and bioavailability of the product as currently proposed. Major concerns also relate to drug formulation containment on the device, disposal of the product, and complexity of system assembly.

I therefore recommend a complete response until the deficiencies are resolved.

1.2 Risk Benefit Assessment

The potential risks of NP101 outweigh its benefits.

There is no new concern about the systemic toxicity of sumatriptan administered transdermally, based on the experience with sumatriptan tablet and subcutaneous

formulation, and the safety data base with the new product. However, we are concerned about the local safety profile and the overall quality of the product. Use of the product has caused significant events at the application site such as third degree burns, severe pain, severe pruritus, and hypersensitivity reactions to name a few. Additionally, there is concern regarding lack of uniformity in the distribution of drug on the medication pad, containment of drug and risk of unintentional exposure, safe disposal procedures, and complex patient usability. Overall, the potential risks of NP101, as currently designed and packaged, outweigh its clinical benefit.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

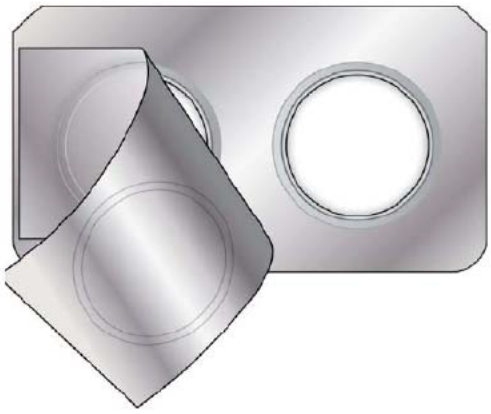
The sponsor seeks approval of a novel, single-use, disposable, co-packaged drug/device combination product that delivers sumatriptan through the transdermal route utilizing iontophoretic technology. The application is submitted in accordance with Section 505(b)(2) of the Food, Drug and Cosmetic Act. The reference for the safety and efficacy of the product is based on GlaxoSmithKline's products: Imitrex® (sumatriptan succinate) Injection (NDA 020080, 1992), Imitrex® (sumatriptan succinate) Tablets (NDA 020132, 1995), and Imitrex® (sumatriptan) Nasal Spray (NDA 020626, 1997). The product is intended for the treatment of acute migraine in adults.

2.1 Product Information

Description of the product
The product, NP101, is a co-packaged drug and device combination product in a transdermal electrode patch. Sumatriptan, the active drug in NP101, is delivered transdermally through an iontophoretic process. Iontophoresis is a drug delivery system that utilizes low electrical current to transfer ionized drug across the skin to underlying tissue and blood vessels.

The drug portion of the transdermal electrode patch consists of two reservoirs. One reservoir contains a pad treated with (b) (4) grams of sumatriptan formulation (polyamine gel with (b) (4) sumatriptan succinate containing 86 milligrams of sumatriptan). The other reservoir contains a pad treated with (b) (4) grams of salt formulation (hydroxypropylcellulose [HPC] with (b) (4) sodium chloride). See Figure 1 Drug Reservoir.

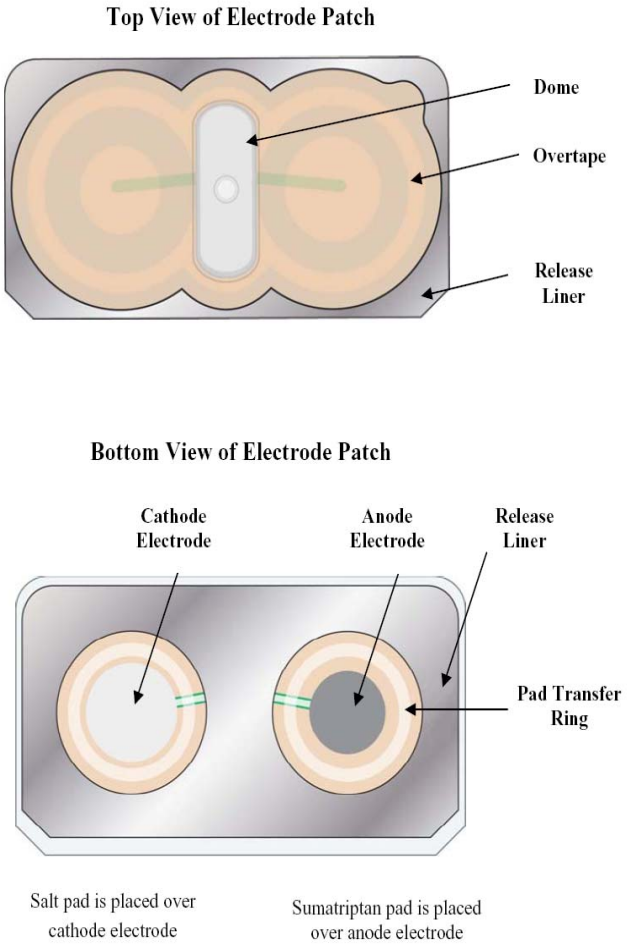
Figure 1 Drug Reservoir



Source: NDA 208,278 submission; Module 2.5, page 8.

The device portion of the product is referred to by the sponsor as the Electrode Patch (E-Patch). It's a single-use, disposable, iontophoretic transdermal patch. The sponsor reports that the device is classified under 21 CFR 890.5525, iontophoresis device. As discussed by the sponsor, the E-Patch consists of two electrodes; a positively charged (b) (4) electrode (anode), and a negatively charged (b) (4) electrode (cathode). The electrodes are connected to a (b) (4) circuit which is powered by two lithium batteries. A plastic dome covers the circuit and batteries. A flexible tape material (referred to as over tape by the sponsor is similar to a flexible bandage) is laminated to the back of the electrode. This helps hold the patch in place when it's applied to the skin. A schematic representation of the E-Patch is presented in Figure 2 Electrode Patch (Top and Bottom View).

Figure 2 Electrode Patch (Top and Bottom View)



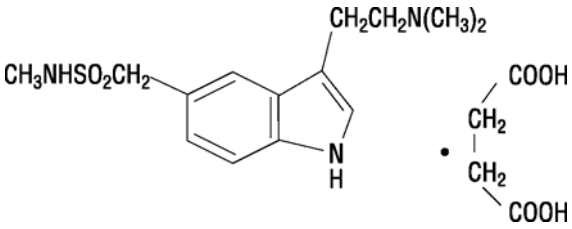
Source: NDA 208,278 submission; Module 2.5, page 9.

The reservoir card and the E-Patch are packaged together. In order to use the product, the top foil on the reservoir card has to be peeled off and removed. This exposes the treated pads of the reservoir cards. The package is then closed which places the treated pads against the electrodes. The sumatriptan-treated pad aligns on the anode portion of the device and the salt-treated pad aligns on the cathode portion of the E-Patch. Pressure is then applied on the back of the reservoir card to transfer the pads onto the respective electrodes. The patch is then removed from the packaging, the release liner is peeled off, and the patch is applied to the upper arm or thigh region of the body. Once applied to the skin, a button on the patch has to be pressed in order to activate the patch. A red light turns on indicating that the patch has been activated. An electrical potential across the electrodes moves the ionized sumatriptan molecules through the skin and into the tissue where they will be absorbed by underlying blood vessels.

Once activated, the total time of drug delivery is four hours. The patch is automatically deactivated at four hours by firmware that is programmed within the device. In a four hour application, 6.5 mg of sumatriptan will be delivered to the patient.

Established name and proposed trade name
The product's established name is sumatriptan iontophoretic transdermal system. The proposed trade name of the product, Zelrix™, was submitted to the agency for review on 17th December, 2010.

Chemical class
The active component of the product is sumatriptan succinate. It is chemically designated as 3-[2-(dimethylamino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate (1:1). The empirical formulation of sumatriptan succinate is $C_{14}H_{21}N_3O_2S \bullet C_4H_6O_4$ and it has a molecular weight of 413.5. The chemical structure of sumatriptan succinate is shown below.



Pharmacologic class
Sumatriptan is a selective 5-hydroxytryptamine1 (5-HT1) agonist. It selectively activates vascular 5-HT1 receptor sites, causing vasoconstriction of intracranial arteries.

Proposed indications, dosing regimens, age groups
The proposed indication for NP101 is for acute treatment of migraine attacks, with or without aura, in adults. It is designed as a single-use, disposable transdermal patch. Each patch delivers 6.5 mg of sumatriptan transdermally over a 4 hour period. One NP101 patch, self-applied to the upper arm or thigh, is the recommended adult dose. The maximum dose that may be given in a 24 hour period is two patches. The second patch should be separated by 2 hours after initial patch activation. The safety and effectiveness of the product has not been established in patients less than 18 years of age and its use in that population is not recommended.

2.2 Tables of Currently Available Treatments for Proposed Indications

The following table summarizes medications used to treat migraine. However, most are not FDA approved for a migraine indication.

Table 1 Acute Migraine Therapies in Current Use [a]

Group 1 [b]	Group 2 [c]	Group 3 [d]	Group 4 [e]	Group 5 [f]
COPYRIGHT MATERIAL				

[a] Table modified from: Silberstein, SD. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;55;754-762.
[b] Proven, pronounced statistical and clinical benefit (at least two double-blind, placebo-controlled studies and clinical impression of effect).
[c] Moderate statistical and clinical benefit (one double-blind, placebo-controlled study and clinical impression of effect).
[d] Statistically but not proven clinically *or* clinically but not proven statistically effective (conflicting or inconsistent evidence).
[e] Proven to be statistically or clinically ineffective (failed efficacy versus placebo).
[f] Clinical and statistical benefits unknown (insufficient evidence available).

The following are FDA approved medications used for treating migraine:

Table 2 FDA Approved Migraine Therapies in Current Use

Brand Name	Generic Name	Manufacturer	Indication
Amerge tablets	naratriptan hydrochloride	GlaxoSmithKline	acute treatment of migraine
Axert tablets	almotriptan malate	Ortho-McNeil Neurologics	acute treatment of migraine
Frova tablets	frovatriptan succinate	Endo Pharmaceuticals	acute treatment of migraine
Imitrex tablets, injection, nasal spray	sumatriptan succinate	GlaxoSmithKline	acute treatment of migraine
Maxalt tablets and Maxalt-MLT orally disintegrating tablets	rizatriptan benzoate	Merck	acute treatment of migraine
Migranal nasal spray	dihydroergotamine mesylate	Valeant	acute treatment of migraine
Relpax tablets	eletriptan hydrobromide	Pfizer	acute treatment of migraine
Sumavel DosePro injection	sumatriptan succinate	Zogenix	acute treatment of migraine
Zomig tablets. nasal spray; and Zomig-ZMT orally disintegrating tablets	zolmitriptan	AstraZeneca	acute treatment of migraine
Blocadren tablets	timolol maleate	Merck	prevention of migraine
Depakote ER tablets	divalproex sodium	Abbott Laboratories	prevention of migraine
Inderal tablets, capsules	propranolol hydrochloride	AstraZeneca	prevention of migraine
Topamax tablets, sprinkle capsules	topiramate	Ortho-McNeil Neurologics	prevention of migraine
Over-the-Counter Products			
Advil Migraine capsules	ibuprofen	Wyeth Consumer Healthcare	treatment of migraine
Excedrin Migraine tablets, caplets	acetaminophen, aspirin, caffeine	Novartis Consumer Health	treatment of migraine
Motrin Migraine Pain caplets	ibuprofen	McNeil Consumer & Specialty Pharmaceuticals	treatment of migraine

Source: Adapted from Consumer Magazine, 2006

The majority of FDA approved migraine products are the triptans, summarized in Table 3.

Table 3 Triptan Therapies Approved for Acute Migraine Treatment in the US

Trade (Generic) Name	NDA	Date of FDA Approval	Route of Delivery
IMITREX® Injection (sumatriptan)	20-080	December 12, 1992	Subcutaneous injection
IMITREX® Tablets (sumatriptan)	20-132	June 1, 1995	Tablet
IMITREX® Nasal Spray (sumatriptan)	20-626	August 26, 1997	Nasal spray
Zomig® (zolmitriptan)	20-768	November 25, 1997	Tablet
Amerge® (naratriptan)	20-763	February 10, 1998	Tablet
Maxalt® / Maxalt-MLT® (rizatriptan)	20-864 / 20-865	June 29, 1998	Tablet / orally dissolving tablet
Zomig-ZMT® (zolmitriptan)	21-231	February 13, 2001	Orally dissolving tablet
Axert® (almotriptan)	21-001	May 7, 2001	Tablet
Frova® (frovatriptan)	21-006	November 8, 2001	Tablet
Relpax® (eletriptan)	21-016	December 26, 2002	Tablet
Zomig® (zolmitriptan)	21-450	September 30, 2003	Nasal spray
Sumavel® DosePro (sumatriptan)	22-239	July 15, 2009	Subcutaneous injection

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient in this transdermal formulation is sumatriptan. It was first approved in 1992 under the trade name Imitrex® (NDA 20-080) by GlaxoSmithKline. Sumatriptan is widely available in the United States in various formulations including tablets, nasal spray and subcutaneous injection. The following is a listing of all currently available formulations of sumatriptan in the United States:

- Oral tablets (GlaxoSmithKline and generics): 25, 50, and 100 mg oral tablets containing sumatriptan succinate
- Oral fixed dose combination (GlaxoSmithKline): Treximet® oral tablets containing 85 mg sumatriptan succinate and 500 mg naproxen
- Nasal spray (GlaxoSmithKline and generics): 5 and 20 mg nasal spray containing sumatriptan succinate

- Subcutaneous injection (GlaxoSmithKline and generics): 4 mg (8 mg/mL) and 6 mg (12 mg/mL) containing sumatriptan succinate

2.4 Important Safety Issues with Consideration to Related Drugs

The safety profile of sumatriptan in patients with a clear diagnosis of migraine or cluster headache has been established. While generally recognized as safe and effective, there have been concerns regarding cardiac complaints. Fatalities have been reported within the triptan class due to cardiac causes. While perhaps vasospastic origin, the phenomenon remains pathologically undefined. Cerebrovascular events and fatalities have also been described, but this relationship is confounded by the presence of these complications in the migraine population in general. Other (non-coronary artery) vasospasm-type events have been described with triptan use including peripheral vascular and colonic ischemia and (rarely) transient and permanent blindness. A precise, clear relationship of these complications to the therapy, accompanied by an understanding of the pathophysiology, remains elusive, again reflecting the background migraine condition. The incidence of all of these disorders remains low when the widespread use of triptans is considered.

Nevertheless because of the risk of myocardial ischemia and/or infarction and other adverse cardiac events, the sumatriptan label clearly states that it should not be given to patients with documented ischemic or vasospastic coronary artery disease (CAD). Similarly it should not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation reveals satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The current label acknowledges the sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. The conclusion is that if, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of or consistent with coronary artery vasospasm or myocardial ischemia, triptans should not be administered.

Still further, in patients whose risk factors predict CAD but who have a satisfactory cardiovascular evaluation, the sumatriptan label strongly recommends that the first administration of sumatriptan take place in the setting of a physician's office or similar medically staffed and equipped facility. As a further safeguard, acknowledging cardiac ischemia can occur in the absence of clinical symptoms, the label suggests consideration be given to obtaining an electrocardiogram during the interval immediately following the first use of sumatriptan in these patients with risk factors.

The current label recommends patients who are intermittent long-term users of sumatriptan and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use the drug. In considering this recommendation for periodic cardiovascular evaluation, it is noted that patients with cluster headache are predominantly male and over 40 years of age, which are risk factors for CAD.

The development of a potentially life-threatening serotonin syndrome may occur with triptans, including sumatriptan, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Development of NP101 was performed under IND 74,877. Three meetings were held between NuPathe and the Agency during the development of this product:

- 18 October 2006: Pre-IND meeting
- 24 November 2009: Pre-NDA meeting
- 04 March 2010: Pre-NDA, CMC-specific meeting

Pre-IND Meeting
A meeting prior to the filing of IND 74,877 was held with the sponsor and the Agency on 18 October 2006.

The Agency emphasized that in addition to the proposed primary endpoint of the proportion of subjects who are headache free at 2 hours post-treatment onset, the following co-primary endpoints are also required: the proportion of subjects who are nausea free, photophobia free and phonophobia free at 2 hours. The Agency also noted that at least one positive efficacy study of acceptable design would be required to support approval.

The Dermatology Division was consulted within the Agency regarding specific safety requirements for the development of transdermal patches. Dr. David Kettl from the Division of Dermatologic and Dental Drug Products at the Agency provided his comments in a memorandum on 5 October, 2006. The Agency found the Phase 2 skin sensitization protocol as outlined by the sponsor to be acceptable. However, the Agency emphasized that human dermal safety testing for the product should include cumulative irritation, sensitization, phototoxicity and photoallergenicity testing and that the study should be conducted with at least 200 evaluable subjects, instead of the proposed 140 subjects. The Agency agreed that the human dermal safety studies can be conducted in parallel with the Phase 3 clinical trials. The sponsor proposed to

conduct the irritation evaluation as part of the sensitization study. The Agency asked the sponsor to submit a proposal and justification and the issue will be reviewed with the IND.

Due to the large volume of distribution of sumatriptan (2 L/kg), the sponsor was instructed to include a range of individuals in the Phase 1 or Phase 3 study to assess the possible effect of increased body fat on the exposure or response to sumatriptan after transdermal administration. The sponsor was also informed that prior to approval they will need to establish long term safety of their product. The sponsor will need to provide data on at least 300 patients treating an average of 2 migraine attacks per month for 6 months, and 100 patients treating an average of 2 migraine attacks for 1 year. The sponsor proposed a shorter study but with a higher intensity of use. The FDA agreed to review the proposal.

Pre-NDA Meeting

A meeting prior to the filing of this NDA was held with the sponsor and the Agency on 24 November 2009.

The sponsor had proposed overall number of subjects and migraine exposures for long term safety data that were less than recommended by ICH guidelines. The Agency had requested data on at least 300 subjects that treated an average of 2 migraine attacks per month for six months and 100 subjects that treated an average of two migraine attacks for one year. The sponsor proposed providing data on 300 subjects who treated an average of 3 migraine attacks for six months and 50 subjects who treated an average of 3 migraine attacks for 12 months. This would provide data on 7,200 treatments. The Agency found these proposed numbers acceptable due to the well known safety profile of sumatriptan in other formulations.

The sponsor provided argument that additional Phase 1 cumulative irritation and sensitization studies would not be pertinent. The Agency responded that these studies are recommended for eventual labeling of the product. If, however, the product is known to be sensitizing and an irritant, then it may be reasonably concluded that there will be an adequate safety database from the clinical trials. If this is the case, then the need for provocative dermal safety studies could be waived.

The sponsor had planned on pursuing labeling allowing for the use of a second transdermal patch during a 24 hour period. The Agency responded that in order permit language in the label for a second patch, the sponsor would have to provide evidence of safety and effectiveness of the second patch.

A request to waive pediatric studies was proposed by the sponsor. The Agency denied granting a waiver for pediatric studies stating that the failure of the original sponsor to establish efficacy may have been related to study design issues. Additionally, the

Agency cited that Axert, another triptan, has been approved for use in the pediatric population suggesting that other drugs in this class are safe and effective in the pediatric group. The Agency also noted that a pediatric development plan should be incorporated into the NDA. The sponsor's pediatric plan will be discussed with the Agency's Pediatric Review Committee (PERC) during the NDA review.

Pre-NDA, CMC-specific Meeting
A CMC-specific meeting was held prior to the submission of the NDA on 4 March, 2010. The comments and discussion regarding this meeting as well as CMC-related issues of other meetings are reviewed by Dr. Martha Heimann and can be found in the CMC section of the NDA review.

2.6 Other Relevant Background Information

None submitted and none required.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the submission was acceptable. The NDA was submitted in eCTD format and conformed to CDISC SDTM standards. The information required for the review of the NDA was well-organized, easy to navigate, and complete.

3.2 Compliance with Good Clinical Practices

The sponsor affirms that all studies in the clinical development program were approved by ethics committees or institutional review boards, in compliance with Good Clinical Practice (GCP) standards according to the International Conference of Harmonization (ICH) Guidelines and the Declaration of Helsinki, version 2004. Written informed consent was obtained for all subjects prior to any study related procedure.

The sponsor certifies it did not use the services of any investigators debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

FDA, through its Division of Scientific Investigations (DSI), inspected three sites from two trials. Two of the inspected sites were from the bioequivalence trial, study NP101-

013. These sites composed of a clinical site and an analytical site. The third site selected for inspection was from the pivotal trial, study NP 101-007.

The goals of the FDA inspections were validation of submitted data and compliance of trial activities with FDA regulations. The inspected records at the sites included informed consent forms, source documents, drug accountability records, protocol inclusion and exclusion criteria, randomization procedures, efficacy end points, and documentation of adverse events.

The inspections of the selected sites identified no significant problems to adversely affect data acceptability. Overall, no deviations from regulations were noted at each site inspected. The FDA inspections reports were reviewed and filed by Dr. Antoine El-Hage, DSI Division of the FDA.

3.3 Financial Disclosures

The sponsor disclosed that one investigator received a $30,000 (b) (6) in 2009. The same investigator also received payments of $600 in 2008 and $2,000 in 2009 for (b) (6). This investigator's site recruited (b) (6) subjects (b) (6)) of a total of (b) (6) subjects in the pivotal (b) (6) subjects (b) (6) %) of a total of (b) (6) subjects in the (b) (6) and (b) (6) subjects (b) (6) %) of a total of (b) (6) subjects in the (b) (6) . Post-hoc analyses of the co-primary endpoints were conducted without these subjects' data and the overall results were not affected.

In summary, the sponsor provided required information regarding financial disclosure and there was no evidence that any study investigators had financial arrangements that may have introduced significant bias into the results of this trial.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC review found the fundamental design of NP101 to be unacceptable as currently proposed.

Four major flaws with the design portion of the product were noted that pose potential safety and efficacy concerns. These include lack of uniformity in the distribution of drug

on the medication pad, lack of adequate containment of drug and risk of unintentional exposure, lack of proper disposal procedures of the product, and patient usability concerns. Additionally, there were numerous concerns raised by CMC regarding residual drug, manufacturing processes, specifications and acceptance criteria of components of the patch, analytical methods, stability, and packaging issues. A comprehensive quality risk management was recommended because of the complexity of the product.

The CMC review was performed by Caroline Strasinger, Ph.D. The above comments were presented to the sponsor in a letter during the review process of the NDA and are reprinted below:

The fundamental design of NP101 is not acceptable. Specifications cannot be established per 21.CFR.314.50 to adequately assure identity, strength, quality, purity, potency and bioavailability of the product. A lack of uniformity of drug formulation distribution, and issues with drug formulation containment, safe disposal procedures, and patient usability raise concerns about the safety and efficacy of the product:

1. Lack of uniformity in the distribution of drug formulation on the non-woven pad

It is visually apparent that the amount of drug on the drug containing pad is not evenly distributed. Furthermore, variable amounts of drug remain on the reservoir side after pad transfer. This lack of uniformity may result in variable amounts of drug transferred from the packaging to the patient, which has potential safety and efficacy implications.

2. Lack of drug formulation containment and risk of unintentional exposure

The drug formulation is not contained once the aluminum foil top is removed from the reservoir. The lack of proper containment increases the safety risk of unintentional exposure to patient, health care provider and general public during assembly, application and wear of the system.

3. Lack of proper disposal procedures during and post use

Drug formulation remaining on the foil packaging material after the system is assembled and the large amount of drug remaining in the system after use pose a safety and potential environmental risk due to exposure to the drug if the packaging and used system are not disposed properly.

4. Patient usability questionable

Inadvertent exposure to the formulated drug substance and improper pad placement for the assembled system pose safety risks. Assembly of the system is complicated and multiple attempts to apply the two pads to the transfer rings increase the opportunity for drug formulation exposure.

Given the complexity of the proposed product a comprehensive quality risk management is highly recommended. Refer to the Guidance for Industry: Q9 Quality Risk Management for further information.

In addition to the comments above, ONDQA has identified the following issues that should be addressed for all proposed systems (Additional issues may be identified in the future upon further review):

General Comments

1. Provide adequate information or submit an appropriate letter of authorization allowing reference to a Drug Master File (DMF) for the following:
    - Non-woven pad
    - Transdermal backing (overtape) of the electrode card
    - Release liner of the electrode patch
    - Transfer ring
    - (b) (4) foam laminate
    - Protective blue slip sheet
2. Clarify if the protective slip sheet is an anti-static treated liner.
3. Include information justifying the size of the patch in section 3.2.P.2 Pharmaceutical Development.
4. Accurately describe the intended dose for NP101. It appears that the system is intended to deliver 6.5 mg of sumatriptan base and the strength is described as 6.5 mg of sumatriptan; however, some descriptions in the NDA state that "approximately (b) (4) mg of sumatriptan is delivered."
5. Identify the non-woven pad as part of the drug product and not part of the container closure system.

Residual Drug

In reference to the information provided by the Applicant in response to the 74-Day letter regarding residual drug, clarify the following additional information.

6. The use of the term '(b) (4) should be justified by statistical methods.
7. Provide the volume of the drug formulation and the surface area tested used in the in vitro development studies.
8. Minimize the drug formulation remaining in the reservoir after the system is used and the pads are removed.

Manufacturing Process

9. Assure that (b) (4) and alter the manufacturing flow chart to reflect this.
10. Provide justification for the (b) (4) hold time of the drug formulation.
11. Establish an IPC for (b) (4) per USP <905> of the bulk drug and salt formulations prior to (b) (4).

E-Patch

12. Provide source, brand, amount added, and impurities of the [redacted] added to the adhesive.
13. Provide a description of the manufacturing process and in process-controls for the electrode card. Include details of the adhesive application process, and overtape, transfer ring, and [redacted] foam [redacted] procedures.
14. Establish acceptance limits in the adhesive [redacted] prior to use in the manufacturing of the E-Patch for the following adhesive impurities, [redacted]
15. Determine extractables and leachables of the overtape and [redacted] foam.
16. Establish an intermediate release specification for the adhesive materials in the electrode card manufacturing which includes a test for adhesion, peel from release liner, shear and tack.

Specification

17. Assure that the sample size for each specification test is of statistical significance.
18. Establish a test method and acceptance criterion for crystals and visible particles for the sumatriptan containing and salt containing pads.
19. [redacted] is not an adequate identification test. Establish an appropriate Identification Test, including a congruent identification test that provides fingerprints for the drug and salt pads.
20. Establish a specification and include acceptance criteria for salt content for the salt pad.
21. Establish a specification and include acceptance criteria for appearance of the electrode card.
    - Include an observation for [redacted] of the adhesives.
    - Include appearance of each electrode and lack of surface flaws, such as scratches.
22. Include in specification for Orientation of Components an observation for the presence of the slip-sheet.
23. Establish a specification and acceptance criteria for impurities in the salt pad. Alternatively, provide justification for not testing for impurities in the salt pad.
24. Clarify whether [redacted] is performed on the bulk formulations or the individual patches. USP <905> does not specifically address transdermal systems; therefore, a description of the proposed procedure.

Analytical Methods

25. Modify the sample preparation method for Assay, Uniformity of Dosage Units, Related Substances, and Methylparaben Content, to include only drug formulation of the non-woven pad representing the amount of drug that is physically transferred to the patient. Do not include the drug remaining on the foil top or other portions of the system.

Stability

26. Confirm that all stability data provided utilizes the proposed commercial upper foil [redacted] of the container closure.
27. Establish a test and acceptance criteria for in vitro release on stability.
28. Perform crystal growth studies.
29. Provide stability data or justification for lack of photostability and freeze-thaw studies.
30. Assess the influence of package orientation on stability as it relates to packaging and storage orientation (laying flat, inverted, on edge, etc).
31. Assess the influence of stacking the individual drug product pouches within a single commercial carton and multiple cartons on each other.
32. Provide acceptance criteria for adhesion, tack, shear, and liner release. Acceptance criteria should be data driven. Adhesion and liner release should have both upper and lower limits.
33. Provide information regarding the investigation in the [redacted]
34. For lot 7063718 clarify or discuss the following statements in section 3.2.P.8.1.7:
    - "The manufacturing date of the sumatriptan [redacted] was [redacted] and the reservoir cards were put on stability [redacted]." This would indicate that the hold time for the sumatriptan formulation is [redacted]
    - Explain what is meant by "[redacted]."

Container Closure

35. Assess extractables and leachables for all packaging components.

Labeling of the Drug Product

36. Provide labeling of the transdermal system.
    - Labeling should include the drug product name, total amount of drug, and expected transdermal flux on the backing membrane of the E-Patch.
    - Inks chosen for printing should not interact with any patch components and assessed for potential leachables and extractables.
37. Provide better identification of the components of the drug product.
    - The drug pad and the salt pad should be clearly labeled and the corresponding electrodes labeled to match. This assures that if the E-Patch or the Reservoir Card detach from the [redacted] prior to assembly, the proper pads will be matched to the proper electrodes.

Regarding use-related and medication error risks

We recommend that you conduct a comprehensive risk analysis identifying the use-related and medication error risks with the iontophoretic transdermal patch. The

purpose of a human factors study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users.

We ask that you explicitly demonstrate that all of the use-related risks for this combination product have been successfully mitigated. We expect that the human factors testing that you perform will be aligned with the Human Factors / Usability Testing recommendations, as explained in our Guidance, *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*.

4.2 Clinical Microbiology

Please refer to clinical microbiology review.

4.3 Preclinical Pharmacology/Toxicology

Please refer to non-clinical pharmacology/toxicology review.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

No new data was acquired for this 505(b)(2) study.

4.4.2 Pharmacodynamics

No new data was acquired for the 505(b)(2) study.

4.4.3 Pharmacokinetics

Pharmacokinetic studies were reviewed by Jagan Parepally, Ph.D., from the Office of Clinical Pharmaceutics. The reader is referred to Dr. Parepally's review for details.

5 Sources of Clinical Data

All documents and datasets reviewed for this NDA submission are in electronic form. The path to this information in the CDER Electronic Document Room is:

\\CDSESUB1\EVSPROD\NDA202278\202278.ENX

5.1 Tables of Studies/Clinical Trials

The following are a listing of clinical studies contributing to efficacy and safety data. The table below is reproduced from the sponsor's NDA submission. It also provides the location of the details of each study within the sponsor's submission.

Abbreviations found in the table:

BA = bioavailability
BE = bioequivalence
CSR = clinical study report
h = hour
HPMC = hydroxypropylmethylcellulose
mA = milliamp
min = minutes
PK = pharmacokinetic
(b) (4)
sc = subcutaneous

Table 4 Listing of Clinical Studies and Trials

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	NP101-005	5.3.1.1	Compare the PK of NP101 with currently approved formulations of Imitrex®	Open-label, randomized, single-center, single-dose, 5-way crossover study (2 additional periods added per amendment) vs sumatriptan sc injection, oral tablet, and nasal spray formulations	NP101 (Zelrix™) patch Treatments A, E, F, G sumatriptan succinate in polyamine formulation, applied to upper arm with a 4 h wear time/600 mA min Control treatments: B: 100 mg oral tablet C: 6 mg sc injection D: 20 mg intranasal	25	Healthy	Single dose (up to seven treatment periods)	Complete; Full CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	NP101-013	5.3.1.2	Assess the BE of the NP101 patch used in Study NP101-007 and that intended for commercial use compared to the currently approved oral formulation of Imitrex®	Open-label, randomized, single-center, single-dose, 3-way crossover study (one additional Group added per amendment) vs sumatriptan oral tablet (Imitrex®)	NP101 (Zelrix™) patches containing 86 mg sumatriptan in polyamine formulation, applied to upper arm with a 4 h wear time (b) mA min Group 1: Treatment A: Patch used in NP101-007 (NP101A) Treatment B: Patch for commercial use (NP101B) Treatment C: 100 mg oral tablet Group 2: Treatment A: Patch used in NP101-007 (NP101A) Treatment D: Patch for commercial use (NP101D) Treatment C: 100 mg oral tablet	63	Healthy	Single dose (up to four treatment periods)	Complete; Full CSR
BA	NP101-012	5.3.1.1	Assess the BA of NP101 applied to two different sites; and assess the PK of NP101 in elderly subjects	Group I: Open-label, randomized, single-center, single-dose, 3-way crossover study vs sumatriptan sc injection in subjects 18-45 yrs of age Group II: Open-label, single-center, single-dose study in subjects >65 yrs of age	NP101 (Zelrix™) patch containing 86 mg sumatriptan in polyamine formulation, applied to upper arm (Group I, Treatment A and Group II) or upper thigh (Group I, Treatment B) with a 4 h wear time (b) mA min Control treatment (Group I only): 6 mg sc injection (Imitrex®)	Group I: 25 Group II: 08	Healthy	Group I: single-dose (up to three treatment periods) Group II: single dose	Complete; Full CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	NP101-001	5.3.3.1	Evaluate the PK profile and relative bio-availability of prototype NP101 patches	Open-label, randomized, single-center, single-dose, crossover study vs sumatriptan sc injection and oral tablet	NP101 (Zelrix™) patch treatments (containing (b) mg sumatriptan in aqueous solution) applied to upper back: NP101.01: (b) (4) NP101.02: NP101.03: NP101.04: Control treatments: 6 mg sc injection; 50 mg oral tablet (Imigran FTab)	8	Healthy	Single dose (total of six treatment periods)	Complete; Abbrev. CSR
PK	NP101-002	5.3.3.1	Evaluate the tolerability and PK profile of prototype NP101 patches applied for different wear times and to different body locations	Open-label, randomized, single-center, single-dose, 6-period crossover study vs sumatriptan oral tablet	NP101 (Zelrix™) patch treatments (containing up to (b) mg sumatriptan in aqueous solution): NP101.05: (b) (4) formulation applied to upper back (Period 1) or upper arm (Period 3) (b) (b) formulation applied to upper arm (Period 4) for (b) (4) mA min NP101.06: (b) (4) formulation, upper arm, (b) mA min (Period 5) NP101.06A: (b) (4) formulation, upper arm, (b) mA min (Period 6) Control treatment (Period 2): 50 mg oral tablet (Imigran FTab)	17	Healthy	Single dose (at least two treatment periods)	Complete; Abbrev. CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	NP101-004	5.3.3.1	Evaluate the PK profile of prototype NP101 patches compared to that of oral sumatriptan succinate	Open-label, single-center, single-dose, 5-period crossover study vs sumatriptan oral tablet	NP101 (Zelrix™) patch treatments (containing up to 86 mg sumatriptan in polyamine formulation) applied to upper arm (Treatments A and C) or upper back (Treatments D and E) and with an anode electrode size of 5 cm^2 (Treatment A) or 10 cm^2 (Treatments C, D, and E): A: 630 mA min C: 630 mA min D: 840 mA min E: 600 mA min Control treatment (Treatment B): 100 mg oral tablet (Imigran FTab)	9	Healthy	Single dose (at least two treatment periods)	Complete; Abbrev. CSR
PK	NP101-006	5.3.3.1	Compare the PK profiles among five NP101 patches	Open-label, single-center, single-dose, 5-period crossover study	NP101 (Zelrix™) patch containing 86 mg sumatriptan in polyamine formulation applied to upper arm (Periods 1, 2, 3, 4) or upper thigh (Period 5); with a pad transfer ring (Periods 1, 3, 5) or without a pad transfer ring (Periods 2, 4); and containing either an S Design (Period 1, 2, 5) or C Design (Period 3, 4) microprocessor	4	Healthy	Single dose (total of five treatment periods)	Complete; Full CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Tolera-bility	NP101-014	5.3.3.3	Evaluate the potential of NP101 transdermal patch to cause skin irritation. The secondary objective was to collect patch adherence data, and to assess the PK of sumatriptan.	Randomized, placebo-controlled, repeat patch test study that compares the NP101 patch to a placebo patch	NP101 (Zelrix™) patch containing 86 mg sumatriptan in polyamine formulation, applied to upper arm with a 4 h wear time/600 mA min. and placebo patch containing a salt formulation	10	Healthy/ Acute migraine headache	Maximum 21 days	Complete; Full CSR
PK	NP101-011	5.3.3.3	Compare the PK of NP101 during an acute migraine attack and during a non-migraine period	Open-label, single-center, single-dose, 4-way crossover study (two additional periods added per amendment) vs sumatriptan oral tablet (Imitrex®)	NP101 (Zelrix™) patch containing 86 mg sumatriptan in polyamine formulation applied to the upper arm during a migraine (Periods 3 and 6) or during a non-migraine period (Periods 4 and 5) Control treatment: 50 mg oral tablet administered during a migraine (Period 1) or during a non-migraine period (Period 2)	23	Healthy/ Acute migraine headache	Single dose (up to six treatment periods)	Complete, Full CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	NP101-007	5.3.5.1	Evaluate the efficacy and safety of NP101 for the treatment of acute migraine	Randomized, parallel-group, double-blind, placebo-controlled, multicenter study	NP101 (Zelrix™) patch containing 86 mg sumatriptan in polyamine formulation, applied to upper arm with a 4 h wear time/600 mA min Control treatment: Placebo patch containing a salt formulation	469 (NP101: 234; placebo: 235)	Healthy/ Acute migraine headache	Single dose	Complete, Full CSR
Safety	NP101-008	5.3.5.2	Evaluate the safety and efficacy of NP101 in the treatment of acute migraine over 12 months	Open-label, multicenter study in subjects previously enrolled and treated (patch activation) in Study NP101-007	NP101 (Zelrix™) patch containing 86 mg sumatriptan in polyamine formulation, applied to upper arm or upper thigh with a 4 h wear time/600 mA min	198	Healthy/ Acute migraine headache	Up to six treatments per month (total of 12 months)	Complete; Full CSR
Safety	NP101-009	5.3.5.2	Evaluate the safety of NP101 in the treatment of acute migraine over 12 months	Open-label, multicenter study	NP101 (Zelrix™) patch containing 86 mg sumatriptan in polyamine formulation, applied to upper arm or upper thigh with a 4 h wear time/600 mA min	514	Healthy/ Acute migraine headache	Up to six treatments per month (total of 12 months)	Ongoing, Interim Report

5.2 Review Strategy

The efficacy review is based on one randomized, double-blind, placebo-controlled phase 3 trial: study NP101-007. Details of study NP101-007 and a discussion of efficacy results are provided below. A summary of the efficacy findings are presented in Section 6, Review of Efficacy.

Two other phase 3 trials, studies NP101-008 and NP101-009, were uncontrolled studies and therefore were not evaluated for efficacy. These studies, however, were reviewed for safety along with study NP101-007 and are presented in Section 7, Review of Safety.

Dr. Jingyu Luan from the Biostatistics Division of the Agency performed the statistical analysis for this submission. Applicable portions of her efficacy review have been referenced and incorporated in this review.

5.3 Discussion of Individual Studies/Clinical Trials: Study NP101-007

Title
The Efficacy and Tolerability of NP101, a Sumatriptan Iontophoretic Transdermal Patch, in the Treatment of Acute Migraine: A Randomized, Double-Blind, Placebo-Controlled Study

Trial Design
This was a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study comparing the efficacy and tolerability of NP101 iontophoretic transdermal patch to a placebo iontophoretic transdermal patch in subjects with acute migraine headache. Enrolled subjects were randomized (1:1 ratio) into one of two treatment groups that were stratified by race (white and non-white):

- NP101: iontophoretic transdermal patch designed to deliver 6.5 mg of sumatriptan over a 4-hour period via an electrical current of (b) (4) milliamps (mA) for the first hour and (b) (4) mA for the next 3 hours
- Placebo: iontophoretic transdermal patch containing sodium chloride that is identical in appearance and design to NP101

Subjects in the study treated one migraine headache with a study patch. Just prior to applying the study patch, subjects rated their baseline migraine headache pain severity in a Migraine Study Diary using a 4-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe). The study patch was applied only if the headache pain severity score was 2 or higher. In addition to headache pain, subjects also recorded the presence or absence of associated symptoms such location of headache (unilateral or bilateral), aura, nausea, photophobia, phonophobia, and whether the headache increased with movement.

Rescue medications, analgesics, and antiemetics were not allowed to be taken from 8 hours before to 2 hours after patch activation. Subjects recorded responses to diary questions at the following time points after patch activation: 0.5, 1, 2, 3, 4, 6, 12 and 24 hours (or further depending on skin assessment results).

Primary efficacy endpoint:

- Proportion of subjects who were headache pain free at 2 hours after patch activation

Key secondary efficacy endpoints:

- Proportion of subjects who were nausea free, photophobia free and phonophobia free at 2 hours after patch activation

Other secondary assessments:

- Proportion of subjects who were headache pain free at each time point (0.5, 1, 3, 4, 6, 12 and 24 hours) after patch activation
- Proportion of subjects who experienced headache pain relief at each time point (0.5, 1, 2, 3, 4, 6, 12 and 24 hours) after patch activation

- Proportion of subjects who were nausea free at each time point (0.5, 1, 3, 4, 6, 12 and 24 hours) after patch activation
- Proportion of subjects who were photophobia free at each time point (0.5, 1, 3, 4, 6, 12 and 24 hours) after patch activation
- Proportion of subjects who were phonophobia free at each time point (0.5, 1, 3, 4, 6, 12 and 24 hours) after patch activation
- Proportion of subjects who were migraine free (no headache pain, no nausea, no phonophobia and no photophobia), at two hours after patch activation
- Proportion of subjects with a sustained headache pain free response (defined as 2 to 24 hour period) following patch activation without the use of rescue medication
- Proportion of subjects who did not use rescue medication within a 24 hour period following patch activation

Safety endpoints:

- Incidence of adverse events (AEs)
- Skin irritation assessments
- Electrocardiograms (ECGs)

Key Inclusion Criteria

- Healthy adults (male and female) aged 18 to 65 years
- Diagnosis of migraine headache, with or without aura, as defined in the International Classification of Headache Disorders, 2nd Edition (ICHD-II), sections 1.1 and 1.2.1 for at least 1 year
- Skin site (upper arm or thigh) for patch application that is relatively hair free with no scars, tattoos, scratches, bruises

Key Exclusion Criteria

- History of failure to respond to sumatriptan (ineffective or poorly tolerated)
- History of skin irritation or skin condition such as eczema, psoriasis, or contact dermatitis
- History of cardiovascular disease, epilepsy or current diagnosis of major depressive disorder
- Female who is pregnant, breastfeeding, or not using birth control
- Abnormal lab test parameters, vital signs or electrocardiogram

Study Visits

Each subject completed 3 study visits: screening, randomization and final visit. The table below depicts the schedule of study events.

Table 5 Schedule of Study Events

Activity	Screening Visit	Randomization Visit (within 45 days of screening)	Final Visit (25 – 72 hrs after patch activation)	Unscheduled Follow-up (10 days ± 2 days after Final Visit)
Informed consent	X			
Demographics	X			
Physical exam (including height and weight at screening only)	X	X		
Review concomitant medication	X	X	X	X
Electrocardiogram	X	X	X	
Vital signs (blood pressure, heart rate, temperature, respiratory rate)	X	X		
Clinical chemistry	X			
Hematology	X			
Urine drug screen	X			
Urinalysis	X			
Urine pregnancy test (females only)	X[1]	X[1]	X[1]	
Review inclusion/exclusion criteria	X	X		
Practice patch applied by subject		X		
Assign randomization number by registering subject in IVRS		X		
Affix box label to IVRS Randomization Confirmation form and dispense study patch		X		
Complete diary header information in subject Migraine Study Diary and provide to subject along with timer		X		
Instruct subject on criteria for qualifying study migraine, diary completion, use of timer, review patch application instructions and Study Participant Information Card and self skin assessment		X		
Investigator skin assessment of upper arms	X	X		
Investigator skin irritation score examination (site application area)			X[2]	X[2]
Compliance check			X	
Adverse event check	X	X	X	X
Collection of used and unused patch			X	
Collection and review of subject Migraine Study Diary			X	
Call IVRS to make Final Call Status			X	
Assess eligibility for participation in open-label study, if applicable			X	

[1] All females who are pregnant at screening or randomization visits are excluded from the study. All females who become pregnant during the course of the study must be offered the ability to participate in the sumatriptan pregnancy registry. Downloadable Sumatriptan Pregnancy Registry forms are available at http://www.kendle.com/registries/#Sumatriptan

[2] For subjects who have a skin irritation score ≥1 at the Final Visit the Investigator will schedule a follow-up visit 10 (±2 days) days from the Final Visit to complete another skin irritation examination and will continue to evaluate weekly until the subject has a skin irritation score of zero (0).

(Source: Sponsor's submission; Study Protocol, module 5.3.5.1.4, Table 10.1)

Additional unscheduled weekly visits occurred if the subject had a skin irritation score of ≥ 1 at the final visit. Subjects returned weekly for re-evaluation until the skin irritation score was zero. A copy of the investigator skin irritation evaluation is provided in Table 6. The subject self-examination irritation evaluation was identical to the investigators except that skin redness was used in place of erythema.

Table 6 Investigator Skin Irritation Score

Score	Definition
0	No erythema
1	Minimal erythema
2	Moderate erythema with sharply defined borders
3	Intense erythema with or without edema
4	Intense erythema with edema and blistering/erosion

(Source: Sponsor's submission; Study Protocol, module 5.3.5.1.3, Table 7)

Protocol Amendments
There were 9 amendments made to the protocol. The clinically relevant modifications are presented below.

- 17 July 2009

The protocol was amended to distinguish the following parameters as "key" secondary objectives/efficacy endpoints: proportion of subjects that are nausea free, photophobia free and phonophobia free at 2 hours after patch activation.

- 26 June 2008

The following secondary objective/efficacy endpoint was added to the protocol: "The proportion of subjects who are nausea free at each time point (0.5, 1, 2, 3, 4, 6, 12 and 24 hours) after patch activation"

- 10 February 2009

Primary objectives/efficacy endpoints of the study were changed from the 4 individual endpoints (subjects who are headache pain free, nausea free, photophobia free and phonophobia free at 2 hours after patch activation) to subjects who are headache pain free at 2 hours after patch activation. The endpoints of nausea free, photophobia free and phonophobia free were later made into key secondary endpoints (see above: 17 July 2009 protocol amendment)

- 11 June 2008

The sponsor provided clarification on the process for randomization. The sponsor noted that in the PK study (NP101-005), post-hoc analysis of PK parameters by race (white versus non-white) in subjects treated with NP101 patch revealed that non-white subjects had different PK parameters after patch application compared with white subjects. As a result of the PK differences, the study design of the protocol was amended to include race stratification. Later in the submission process, the sponsor added the following statement in the Clinical Study Report section: "Race stratification was prompted by results from a previous NP101 PK study (NP101-005), which showed a higher AUC and Cmax for sumatriptan in white subjects than non-white subjects after NP101 application."

Statistical Methods for Efficacy Analyses

Logistic regression models were used to evaluate efficacy. The primary efficacy endpoint, the proportion of subjects who were headache pain free at 2 hours after patch activation, utilized treatment group as the main effect and race as a covariate of randomization stratum. A three-factor logistic regression model was used for the key secondary endpoints, the proportion of subjects who were nausea free, photophobia free and phonophobia free at 2 hours after patch activation. In these analyses, treatment group was the main effect of treatment while randomization stratum (race) and baseline score were covariates. Baseline score was added as a second covariate to account for the variability of symptoms at baseline.

All efficacy analyses had adjusted odds ratio (adjusted for covariates) and corresponding 95% confidence intervals (95% CIs) and nominal *p* value for the comparison between the treatment groups (NP101 and placebo) for each endpoint. Efficacy analyses were based on the intent-to-treat (ITT) population. The ITT populations were subjects who applied and activated the study patch and who had at least one post baseline assessment for pain.

Missing values in the primary and key secondary efficacy analyses were imputed using a last observation carried forward (LOCF) method. Two sets of sensitivity analyses, baseline carried forward (BCF) and observed cases (OC), were used to evaluate the impact of missing data imputation method on the conclusion of treatment effect. The primary efficacy analysis of treatment effect used LOCF analysis based on the ITT population for headache pain free at 2 hours after patch activation.

The following covariates and their subgroups were assessed for response to the primary and key secondary efficacy endpoints based on the LOCF imputation for missing data:

- Age: ≤median or >median years
- Gender: male or female
- Race: white or non-white

- BMI : ≤median or >median BMI
- Aura with migraine: presence or absence
- Study center

Trial Populations / Patient Disposition

Study NP 101-007 randomized and enrolled 530 subjects (265 to the NP101 group and 265 to the placebo group) from 38 centers in the United States. The trial was conducted between 12 January 2009 and 06 July 2009.

Of the 530 enrolled subjects, 61 subjects (31 in the NP101 group and 30 in the placebo group) were not treated as they did not apply study patch within 2 months after randomization. The remaining 469 subjects (234 in the NP101 group and 235 in the placebo group) applied the patch and were included in the safety population. The safety population consisted of all subjects who applied a study patch.

Fifteen subjects in the safety population (8 in the NP101 group and 7 in the placebo group) were excluded from the ITT population due to protocol violations. Thus, a total of 454 subjects (226 in the NP101 group and 228 in the placebo group) formed the ITT population. These 454 subjects (96.8% of initially enrolled subjects) made the primary population for analysis of efficacy, as shown in Table 7.

Table 7 Disposition of Subjects in Trial NP101-007

Disposition	NP101	Placebo	Total
Randomized	265	265	530
Randomized, not treated	31	30	61
Safety analysis population[a]	234 (100)	235 (100)	469 (100)
Intent-to-treat analysis population[b]	226 (96.6)	228 (97.0)	454 (96.8)
Per protocol analysis population[c]	220 (94.0)	226 (96.2)	446 (95.1)
Completed study	222 (94.9)	226 (96.2)	448 (95.5)
Discontinued study	12 (5.1)	9 (3.8)	21 (4.5)
Did not experience qualifying migraine headache	0	1 (0.4)	1 (0.2)
Failed/improper functioning study patch	1 (0.4)	4 (1.7)	5 (1.1)
Adverse event	5 (2.1)	3 (1.3)	8 (1.7)
Lost to follow-up	4 (1.7)	1 (0.4)	5 (1.1)
Other	2 (0.9)	0	2 (0.4)

[a] Subjects applied study patch.
[b] Subjects applied and activated study patch with pad transfer and had at least one post baseline assessment for each migraine symptom (pain, photophobia, phonophobia, and nausea).
[c] Intent-to-treat subjects who did not have any major protocol violations as defined prior to database lock.

(Source: Sponsor's submission; Clinical Study Report, Table 10)

Demographics, Background, and Baseline Variables

Demographics and baseline characteristics were well balanced in the two treatment groups in the ITT population. Table 8 summarizes these findings. The safety population also had similar demographics and baseline characteristics as the ITT population.

Overall, the demographics and subject characteristics noted in this trial are typical of other migraine trials, with more females than males, more whites than other races and with a mean subject age of around 40. In this trial, there were 85% more females than males. Approximately, 82% of subjects were white, 15% were black, and the remainders were of other races. Mean body mass index (BMI) was 27 and the mean age was 41.

Table 8 Demographic and Baseline Characteristics of ITT Population

Characteristics	NP101 N=226 (%)	Placebo N=228 (%)	Total N=454 (%)
Age: Mean (SD)	40.7 (11.15)	41.0 (10.99)	40.8 (11.06)
Gender: n (%)			
Male	36 (15.9)	32 (14.0)	68 (15.0)
Female	190 (84.1)	203 (86.0)	398 (85.0)
Race: n (%)			
White	186 (82.3)	184 (80.7)	370 (81.5)
Black (African American)	34 (15.0)	32 (14.0)	66 (14.5)
Asian	3 (1.3)	8 (3.5)	11 (2.4)
American Indian/Alaska Native	2 (0.9)	2 (0.9)	4 (0.9)
Pacific Islander	1 (0.4)	2 (0.9)	3 (0.7)
BMI (kg/m^2): Mean (SD)	27.1 (6.75)	27.0 (6.32)	27.0 (6.53)

(Source: Sponsor's submission; Clinical Study Report, Table 12, page 72; Table 14.1.4.1)

The two treatment groups were also similar in their migraine history profiles. Subjects had a history of migraine headaches for approximately 21 years. The median duration of migraine attacks that were treated lasted for 12 hours. The subjects in the study had an average of 4 headaches a month. The safety population migraine history profile is provided in Table 9.

Table 9 Migraine History in Safety Population

	NP101 N=234 (%)	Placebo N=235 (%)	Total N=469 (%)
Subjects with a migraine history assessment	234 (100)	235 (100)	469 (100)
Years experienced migraine headache (yrs)			
Mean (SD)	21.6 (11.93)	20.6 (11.62)	21.1 (11.77)
Minimum, Maximum	2, 51	1, 49	1, 51
Duration of treated migraine headache (hrs)			
Median	11.0	12.0	12.0
Minimum, Maximum	1, 144	1, 72	1, 144
Average number of migraine headaches per month			
Mean (SD)	3.9 (1.49)	4.0 (1.35)	4.0 (1.42)
Minimum, Maximum	1, 11	1, 6	1, 11
Migraine classification (n [%])			
Migraine headache with aura	15 (6.4)	23 (9.8)	38 (8.1)
Migraine headache without aura	156 (66.7)	135 (57.4)	291 (62.0)
Both	63 (26.9)	77 (32.8)	140 (29.9)

(Source: Sponsor's submission; Clinical Study Report, module 5.3.5.1.3, Table 14)

Protocol Deviations and Violations

As mentioned previously, 15 subjects were excluded from the ITT population (8 in the NP101 group and 7 in the placebo group). Reasons for exclusion related to problems with the patch device as well as lack of post baseline migraine assessments and are presented in Table 10. Problems with the patch occurred in more than 2% of the study population.

Table 10 Exclusion from ITT Population

Analysis Population, N (%)	NP101 N=234 (%)	Placebo N=235 (%)	Total N=469 (%)
Safety analysis population	234 (100)	235 (100)	469 (100)
Intent-to-treat analysis population	226 (96.6)	228 (97.0)	454 (96.8)
Not included in the intent-to-treat population:	8 (3.4)	7 (3.0)	15 (3.2)
Red LED light did not go solid	3 (1.3)	5 (2.1)	8 (1.7)
No post baseline migraine assessment	3 (1.3)	1 (0.4)	4 (0.9)
Reservoir pads did not transfer	2 (0.9)	1 (0.4)	3 (0.6)

(Source: Sponsor's submission; Clinical Study Report, module 5.3.5.1.3, Table 11)

Efficacy Results

Primary Efficacy Endpoint

The proportion of subjects who were headache pain free at 2 hours after patch activation was the primary efficacy endpoint.

There was a significantly greater proportion of subjects who were headache pain free at 2 hours post treatment in the NP101 group than in the placebo group (17.7% versus 9.2%, *p*=0.0092). Of the 226 subjects in the ITT population who were in the NP101 treatment group, 40 subjects (17.7%) reported having no headache pain at 2 hours after patch activation. In the placebo group, 21 out of the 228 subjects (9.2%) reported no headache pain at 2 hours after patch activation. This 8.5% difference between the two groups was statistically significant (Table 11).

There was very little data that was missing when evaluating the primary endpoint. Analyses based on observed cases (OC) and baseline carried forward (BCF) had similar results as the primary method of analysis, the last observation carried forward (LOCF).

Table 11 Primary Efficacy Endpoint in ITT Population

Two Hours After Patch Activation	Number (%) Subjects		Treatment Difference (%)	Logistic Regression Analysis[a]	
	NP101 N=226 (%)	Placebo N=228 (%)		Odds Ratio (95%CI)	*p* value
Headache pain free – LOCF analysis	40/226 (17.7)	21/228 (9.2)	8.5	2.1 (1.20, 3.72)	0.0092
Headache pain free – OC analysis	40/225 (17.8)	21/227 (9.3)	8.5	2.1 (1.20, 3.72)	0.0092
Headache pain free – BCF analysis	40/226 (17.7)	21/228 (9.2)	8.5	2.1 (1.20, 3.72)	0.0092

LOCF = Last Observation Carried Forward.
OC = Observed Cases.
[a] The logistic regression model for headache free includes main effect of treatment and a covariate of randomization stratum. Odds ratio is the ratio of the odds to be a responder after treating with a NP101 patch vs. treating with a placebo patch.

(Source: Sponsor's submission; Clinical Study Report, module 5.3.5.1.3, Table 17)

Two subjects in the placebo group used rescue medication before the 2 hour headache assessment time point. They were not included as responders for the primary endpoint and were treated as failures for the primary analysis.

Key Secondary Efficacy Endpoints

The proportion of subjects who were nausea free, photophobia free, and phonophobia free at 2 hours after patch activation were the key secondary efficacy endpoints.

The sponsor reported significantly greater proportion of subjects who were nausea free, photophobia free, and phonophobia free in the NP101 group compared to placebo group at 2 hours after patch activation (Table 12). The greatest difference between the two treatment groups among the key secondary efficacy endpoints occurred in the nausea free endpoint. There was significant improvement of nausea starting as early as 1 hour after patch activation in the NP101 group compared to placebo group. Analyses based on OC and BCF had similar results as the primary method of analysis, LOCF.

Table 12 Key Secondary Efficacy Endpoints in ITT Population

Two Hours After Patch Activation	Number (%) Subjects		Treatment Difference (%)	Logistic Regression Analysis[a] Odds Ratio (95%CI)	*p* value
	NP101 N=226 (%)	Placebo N=228 (%)			
Photophobia free	116 (51.3)	83 (36.4)	14.9	1.9 (1.24, 2.86)	0.0028
Phonophobia free	125 (55.3)	89 (39.0)	16.3	2.2 (1.46, 3.40)	0.0002
Nausea free	189 (83.6)	144 (63.2)	20.4	3.0. (1.84, 4.83)	<0.0001

[a] The logistic regression models for photophobia, phonophobia, and nausea free include the main effect of treatment and two covariates of randomization stratum and baseline score. Odds ratio is the ratio of the odds to be a responder after treating with a NP101 patch vs. treating with a placebo patch.

(Source: Sponsor's submission; Clinical Study Report, module 5.3.5.1.3, Table 18)

Other Endpoints

Other secondary assessments of efficacy included:

- Proportion of subjects who were headache pain free at each time point (0.5, 1, 3, 4, 6, 12 and 24 hours) after patch activation
- Proportion of subjects who experienced headache pain relief at each time point (0.5, 1, 2, 3, 4, 6, 12 and 24 hours) after patch activation
- Proportion of subjects who were nausea free at each time point (0.5, 1, 3, 4, 6, 12 and 24 hours) after patch activation
- Proportion of subjects who were photophobia free at each time point (0.5, 1, 3, 4, 6, 12 and 24 hours) after patch activation
- Proportion of subjects who were phonophobia free at each time point (0.5, 1, 3, 4, 6, 12 and 24 hours) after patch activation
- Proportion of subjects who were migraine free (no headache pain, no nausea, no phonophobia, and no photophobia), at two hours after patch activation
- Proportion of subjects with a sustained headache pain free response (defined as 2 to 24 hour period) following patch activation without the use of rescue medication
- Proportion of subjects who did not use rescue medication within a 24 hour period following patch activation

There was a numerical difference between the two treatment groups in all the secondary efficacy analyses noted above.

Headache Pain Free Response by Time Point

The results of analyses of the proportion of subjects who were headache pain free at each time point after patch activation are presented in Table 13. A numeric treatment effect is noted from the 2 hour time point to the 12-hour time point. At the 2 hour time point, 17.7% of subjects in the NP101 treatment group and 9.2% of subjects in the placebo group were headache pain free. By the 24 hour time point, 70.7% of subjects in the NP101 treatment group and 70.3% in the placebo group were headache pain free.

Table 13 Headache Pain Free Response by Time Point

Time point	NP101 N=226 (%)	Placebo N=228 (%)	% Difference (NP101-placebo)
0.5 hour	1/226 (0.4)	0/228 (0.0)	0.4
1 hour	14/225 (6.2)	8/227 (3.5)	2.7
2 hours	40/226 (17.7)	21/228 (9.2)	8.5
3 hours	69/225 (30.7)	37/227 (16.3)	14.4
4 hours	103/224 (46.0)	53/227 (23.3)	22.7
6 hours	124/223 (55.6)	86/226 (38.1)	17.5
12 hours	152/224 (67.9)	130/222 (58.6)	9.3
24 hours	157/222 (70.7)	156/222 (70.3)	0.4

(Source: Sponsor's submission; Clinical Study Report, module 5.3.5.1.3, Table 19)

Nausea Free by Time Point

The analysis of proportion of subjects who were nausea free was similar to other secondary endpoints. A numeric treatment effect was noted from the one hour time point to the 12 hour time point. Table 14 summarizes the treatment effect on nausea by measured time points.

Table 14 Nausea Free Response by Time Point

Time point	NP101 N=226 (%)	Placebo N=228 (%)	% Difference (NP101-placebo)
0.5 hour	138/225 (61.3)	122/228 (53.5)	7.8
1 hour	160/225 (71.1)	131/227 (57.7)	13.4
2 hours	189/226 (83.6)	144/228 (63.2)	20.4
3 hours	193/223 (86.5)	158/226 (69.9)	16.6
4 hours	207/223 (92.8)	172/227 (75.8)	17.0
6 hours	207/218 (95.0)	184/225 (81.8)	13.2
12 hours	213/219 (97.3)	200/222 (90.1)	7.2
24 hours	207/219 (94.5)	202/220 (91.8)	2.7

(Source: Sponsor's submission; Clinical Study Report, module 5.3.5.1.3, Table 21)

A similar pattern also emerged when subjects were evaluated for photophobia and phonophobia by time point. A numeric treatment effect was noted for both photophobia and phonophobia from the 2 hour time point to the 12 hour time point. The proportion of subjects who were photophobia free by 4 hours was 76.2% in the NP101 group versus 51.1% in the placebo group (Table 15). By 24 hours, there was only a 1.8% difference between the two groups with 85.4% of the NP101 being photophobia free compared to 83.6% of the placebo group.

Table 15 Photophobia Free Response by Time Point

Time point	NP101 N=226 (%)	Placebo N=228 (%)	% Difference (NP101-placebo)
0.5 hour	48/226 (21.2)	38/227 (16.7)	4.5
1 hour	74/225 (32.9)	63/227 (27.8)	5.1
2 hours	116/226 (51.3)	83/228 (36.4)	14.9
3 hours	155/224 (69.2)	103/227 (45.4)	23.8
4 hours	170/223 (76.2)	116/227 (51.1)	25.1
6 hours	181/217 (83.4)	143/224 (63.8)	19.6
12 hours	194/218 (89.0)	176/221 (79.6)	9.4
24 hours	187/219 (85.4)	184/220 (83.6)	1.8

(Source: Sponsor's submission; Clinical Study Report, module 5.3.5.1.3, Table 22)

Likewise, the phonophobia free response by time point showed that at 4 hours 77.1% of the NP101 treatment group was phonophobia free compared to 59.5% in the placebo group. By 24 hours, 90% of the NP101 were photophobia free versus 85.4% of the placebo group (Table 16).

Table 16 Phonophobia Free Response by Time Point

Time point	NP101 N=226 (%)	Placebo N=228 (%)	% Difference (NP101-placebo)
0.5 hour	61/226 (27.0)	58/227 (25.6)	1.4
1 hour	87/225 (38.7)	81/227 (35.7)	3.0
2 hours	125/226 (55.3)	89/228 (39.0)	16.3
3 hours	160/224 (71.4)	118/227 (52.0)	19.4
4 hours	172/223 (77.1)	135/227 (59.5)	17.6
6 hours	188/217 (86.6)	152/225 (67.6)	19.0
12 hours	199/218 (91.3)	177/222 (79.6)	11.6
24 hours	197/219 (90.0)	187/219 (85.4)	4.6

(Source: Sponsor's submission; Clinical Study Report, module 5.3.5.1.3, Table 23)

Use of Rescue Medication

The proportion of subjects who did not use rescue medication in a 24 hour period after patch activation was higher in the NP101 group compared to the placebo group. At 24 hours after patch activation, 60% of the NP101 group had not used rescue medication compared to 40% of the placebo group. By 3 hours after patch activation and continuing to 24 hours, there were progressively more subjects in the placebo group than in the NP101 group that used rescue medication. The results are provided in Table 17.

Table 17 Proportion of Subjects that Used Rescue Medication

Time Point	NP101 N=226 (%)	Placebo N=228 (%)
0.5 Hour	0/226 (0)	1/228 (0.4)
1 Hour	0/226 (0)	2/228 (0.9)
2 Hours	0/226 (0)	2/228 (0.9)
3 Hours	36/226 (15.9)	57/228 (25.0)
4 Hours	44/226 (19.5)	76/228 (33.3)
6 Hours	57/226 (25.2)	105/228 (46.1)
12 Hours	66/226 (29.2)	125/228 (54.8)
24 Hours	90/226 (39.8)	136/228 (59.6)

(Source: Sponsor's submission; Clinical Study Report, module 5.3.5.1.3, Table 24)

Subpopulations

Dr. Jingyu (Julia) Luan, from the Division of Biometrics at the FDA, conducted subgroup analyses based on age, race and gender for the primary and key secondary endpoints. Tables 18-21 (reproduced from Dr. Luan's review) are presented below.

Table 18 Summary of Subgroup Analysis of Headache Pain Free: LOCF Analysis for ITT Population

Subgroup	NP101: Number (%)	Placebo: Number (%)
Age Group		
<=41 yrs	10 (9)	7 (6)
>41 yrs	30 (25)	14 (12)
Race Group		
White	35 (19)	16 (9)
Non-white	5 (13)	5 (11)
Sex		
Male	4 (11)	3 (9)
Female	36 (19)	18 (9)

(Source: Statistical reviewer's analysis)

Table 19 Summary of Subgroup Analysis of Photophobia Free: LOCF Analysis for ITT Population

Subgroup	NP101: Number (%)	Placebo: Number (%)
Age Group		
<=41 yrs	46 (43)	35 (31)
>41 yrs	70 (59)	48 (42)
Race Group		
White	97 (52)	67 (36)
Non-white	19 (48)	16 (36)
Sex		
Male	16 (44)	15 (47)
Female	100 (53)	68 (35)

(Source: Statistical reviewer's analysis)

Table 20 Summary of Subgroup Analysis of Phonophobia Free: LOCF Analysis for ITT Population

Subgroup	NP101: Number (%)	Placebo: Number (%)
Age Group		
<=41 yrs	58 (54)	37 (32)
>41 yrs	67 (57)	52 (46)
Race Group		
White	103 (55)	74 (40)
Non-white	22 (55)	16 (36)
Sex		
Male	22 (61)	15 (47)
Female	103 (54)	74 (38)

(Source: Statistical reviewer's analysis)

Table 21 Summary of Subgroup Analysis of Nausea Free: LOCF Analysis for ITT Population

Subgroup	NP101: Number (%)	Placebo: Number (%)
Age Group		
<=41 yrs	90 (83)	69 (61)
>41 yrs	99 (84)	75 (66)
Race Group		
White	156 (84)	111 (60)
Non-white	33 (83)	33 (75)
Sex		
Male	32 (89)	18 (56)
Female	157 (83)	126 (64)

(Source: Statistical reviewer's analysis)

For the subpopulation analyses, Dr. Luan concludes that "the point estimates of the treatment effects are all in the same direction. However, it appears that the proportion of subjects who were headache pain free in the NP101 group was numerically larger than that in placebo group."

I have reviewed the subgroup analyses and find efficacy in non-white subjects to be in question. The 2-hour pain free rate in both NP101 group and placebo group is essentially the same (Table 22).

Table 22 Summary of Subgroup Analysis of Headache Pain Free: LOCF Analysis for ITT Population

Subgroup	NP101: Number (%)	Placebo: Number (%)
Race Group		
White	35 (19)	16 (9)
Non-white	5 (13)	5 (11)

(Source: Adapted from statistical reviewer's analysis)

Overall, from the information provided, efficacy in non-white subjects for the primary endpoint (headache pain freedom at 2 hours) has not been adequately demonstrated.

6 Review of Efficacy

Efficacy Summary

Review of the efficacy data revealed the following major findings:

- The sponsor has adequately demonstrated a statistically significant superiority of NP101 over placebo in the primary and key secondary endpoints

- There is inadequate information to support efficacy of the product in non-white subjects

The review of efficacy for NP101 was based on one controlled, randomized, phase 3 trial: Study NP101-007, "The efficacy and tolerability of NP101, a sumatriptan iontophoretic transdermal patch, in the treatment of acute migraine: A randomized, double-blind, placebo-controlled study". Two other phase 3 trials submitted by the sponsor (studies NP101-008 and NP101-009) were uncontrolled studies and therefore were not evaluated for efficacy. These trials were reviewed for safety and are presented in Section 7 (Review of Safety).

The pivotal trial, Study NP101-007, is reviewed in detail for efficacy in Section 5.3.1 above. The findings are summarized in this section for the reader's convenience.

6.1 Indication

The proposed labeling for NP101 is for the acute treatment of migraine headache with or without aura in adults.

6.1.1 Methods

A double blind, parallel-group, single dose trial of NP101 transdermal patch versus placebo patch in adult migraineurs was performed. Subjects treated one migraine headache of moderate to severe intensity with a study patch. They documented their headache pain and associated symptoms in a diary at designated time points from start of migraine to 24 hours. Use of rescue medications to treat pain or nausea was allowed after the first 2 hours of patch activation. Efficacy analyses were based on logistic regression models. For the primary endpoint, treatment group was a main effect and randomization (race) was a covariate. A three-factor model was used to analyze key secondary endpoints: treatment group was a main effect, randomization stratum (race) was a covariate and the baseline value of the symptom was a second covariate. Missing values were imputed using a last observation carried forward method.

6.1.2 Demographics

The treatment population closely modeled parameters which describe the usual migraine population found in the community as well as other migraine trials. The average age of subjects was 41 years. Female subjects formed the majority of participants at 85%. Approximately 82% of the subjects were white and 15% were black.

6.1.3 Subject Disposition

530 subjects initially enrolled in the trial but 61 of these subjects were removed from the study as they did not apply the patch within the designated 2 month timeframe from randomization. The remaining 469 subjects formed the safety population (234 in the NP101 treatment group and 235 in the placebo group). 15 subjects in the safety population (8 in the treatment group and 7 in the placebo group) were excluded from the efficacy analysis due to violations such as device malfunction or not having a baseline migraine assessment. The remaining 454 subjects formed the ITT population, which was the primary analysis of efficacy.

6.1.4 Analysis of Primary Endpoint

The primary endpoint was the proportion of subjects who were headache free at 2 hours after transdermal patch activation. There was an 8.5% treatment difference between the NP101 treatment group compared to the placebo group. The *p*-value is 0.0092.

The primary and key secondary endpoints selected for this trial conformed to Agency requirements in support of efficacy. These endpoints were also consistent with efficacy endpoints in other migraine trials. Overall, the sponsor adequately demonstrated a statistically significant difference between the NP101 treatment group and the placebo group.

6.1.5 Analysis of Key Secondary Endpoints

The key secondary endpoints were the proportion of subjects who were nausea free, photophobia free and phonophobia free at 2 hours after patch activation. There were statistically significant differences between the two groups. Treatment differences between NP101 group and placebo group for nausea free, photophobia free and phonophobia free at 2 hours after patch activation were 20.4%, 14.9% and 16.3%, respectively.

These key secondary endpoints, also referred to as co-primary endpoints in other migraine trials, conformed to Agency requirements in support of efficacy. As in the primary endpoint, there was a statistically significant difference between the two treatment groups.

6.1.6 Other Endpoints

Secondary endpoints assessed in the trial included headache pain severity, presence or absence of nausea, photophobia and phonophobia, and use of rescue medications at various time points from baseline to 24 hours after patch activation. There was a numerical difference between the two treatment groups in all the secondary efficacy endpoints analyzed.

6.1.7 Subpopulations

Subgroup analyses were conducted based on age, race and gender for the primary and key secondary endpoints. Efficacy of the product for the primary endpoint in non-white subjects was not adequately demonstrated. The 2-hour headache pain-free rate for non-white subjects in both the NP101 group and placebo group was essentially the same.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The device, iontophoretic transdermal patch, is designed to deliver 6.5 mg of sumatriptan over a 4 hour period transdermally. The dose of sumatriptan selected is similar to the listed reference drug (Imitrex subcutaneous injection).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Due to the short term nature of this trial, no comment may be made upon persistence of therapeutic efficacy or tolerance effects of NP101.

6.1.10 Additional Efficacy Issues/Analyses

No additional pre-specified efficacy issues or analyses were performed.

7 Review of Safety

Safety Summary

Review of the safety data revealed the following major concerns:

- Number of NP101 transdermal patch exposures by subjects in the long term trials was less than the exposures agreed upon with the Agency
- There is significant irritation potential of NP 101 transdermal patch with high incidence of application site conditions
- Inadequate information on skin adverse reactions (e.g., use of non-specific terms such site reactions or adverse drug reactions) and on final outcome of skin adverse reactions (e.g., skin discoloration, burns)
- Inadequate information on reasons for treatment discontinuations/withdrawal of consent
- Inadequate information about minimal time between 2 applications of the patch at the same site

Adverse events were predominantly due to application site conditions. Almost half of all subjects in the safety population (376/796, 47%) had an application site adverse event. Application site reaction, pain, and pruritus were the most common AEs in the efficacy study (NP101-007). The long term safety studies (NP101-008 and NP101-009) also had AEs due to allergic contact dermatitis (delayed hypersensitivity reaction) from NP101 application.

There was a high rate of severe skin reactions from patch application. Of the 796 subjects in the Phase 3 studies (NP101-007, 008, and 009) who applied at least 1 patch, 43 (5.4%) sustained a severe adverse event. There were 3 cases of severe skin burns and 1 case of severe skin discoloration from patch application. Details of these specific severe adverse and outcomes of these events were not readily available in the submission.

Over half of the subjects in the long term trials discontinued from the studies. The rate of discontinuations and withdrawal of consent was much higher than noted in other migraine trials. Withdrawal of consent and AEs constituted the most common reasons for discontinuation. Reasons for withdrawal of consent were not adequately provided. Adverse events that led to discontinuations were predominantly due to patch site conditions.

There were no deaths reported in the clinical trials. A total of 11 SAEs were reported in the Phase 3 clinical trials and the 120 Day Safety Update. None of these events were related to treatment. Analysis of the safety data indicates that there is no need to consider a postmarketing risk evaluation and mitigation strategy (REMS) at this time.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The sponsor reported that 978 subjects participated in 12 clinical trials during the development program of NP101. A summary of all the trials is presented in Table 4 above. Of the total number of enrolled subjects, 182 received NP101 patch treatment in Phase I trials and 796 subjects received NP101 patches in the Phase 3 trials.

The following points, provided by the sponsor, highlight the clinical trials conducted and subject participation for the NDA submission:

- Three initial Phase 1 tolerability and pharmacokinetic studies (NP101-001, NP101-002, and NP101-004) using prototype NP101 patches were conducted in The Netherlands. A total of 34 healthy subjects received patch applications in these studies.

- Subsequent Phase 1 studies using the final NP101 patch configuration (sumatriptan and salt formulations, electrodes, and wave form) were conducted in the United States (Studies NP101-005, NP101-006, NP101-011, NP101-012, NP101-013, and NP101-014). A total of 129 healthy subjects and 19 subjects with migraine received at least one NP101 patch application in these studies. In these studies, the primary objective was to assess the pharmacokinetics of NP101.

- In a randomized, double-blind, placebo-controlled Phase 3 efficacy and safety study (NP101-007), 234 subjects applied a single NP101 study patch for the treatment of a qualifying migraine headache (235 subjects received a placebo patch).

- Subjects who completed Study NP101-007 were eligible to enroll in Study NP101-008, in which the long term efficacy and safety of NP101 (up to six treatments per month for up to 12 months) was assessed. A total of 183 subjects used (applied and activated) a total of 2089 NP101 patches over the 12-month period of this study.

- In a second long term safety study, Study NP101-009, subjects were enrolled to receive open-label NP101 for up to 12 months. This study was ongoing at the time of this submission. As of the interim database lock on 18 October 2010, a total of 479 subjects had used a total of 5562 NP101 patches in this study.

- In summary, 182 unique subjects received NP101 in Phase 1 studies and 796 unique subjects received NP101 in Phase 3 studies.

In order to maintain clarity and avoid redundancy in the safety review, I chose the following strategy in presenting the safety data for NP101. For deaths, serious adverse events, and adverse dropouts, I include information from the safety database of all trials in the development program of NP101. For other safety sections (adverse events, laboratory data, vitals signs, ECG), I present data from the Phase 3 trials. I review safety results from the Phase 1 studies when they deviate in a clinically meaningful way from the results of the major Phase 3 trials, or when the information adds clinical insight into the safety of the product.

Overall, the safety data analyzed in this review were derived primarily from the Phase 3 clinical trials. These trials consisted of one randomized, double-blinded, placebo-controlled trial (Study NP101-007) and two open-label long-term trials (Studies NP101-008 and NP101-009). The database cutoff date was 18 October 2010. The sponsor provided 120-Day Safety Update during the review process is included in the review where appropriate.

7.1.2 Categorization of Adverse Events

The sponsor defined adverse events (AEs) as “an undesirable medical occurrence (sign, symptom, or diagnosis) or worsening of a pre-existing medical condition (e.g., diabetes, congestive heart failure, rheumatoid arthritis, psoriasis) that occurred at any time after signing of the informed consent form whether or not it was considered to be related to NP101”. The sponsor defined treatment emergent adverse events (TEAEs) as any AEs that “occurred after activation of the first patch”.

In addition to the routine exploration of AEs, the sponsor presented additional analyses of selected AEs of particular concern. The sponsor considered allergic contact dermatitis (ACD, delayed hypersensitivity reaction) of special interest because of the potential of NP101 to cause ACD. Subjects deemed to have cases of ACD had their cases reviewed by a dermatology ACD specialist consultant to the sponsor. The subjects were also provided referral for allergy testing to sumatriptan and NP101 medication pads. Further discussion of ACD is presented in section 7.3.4, Significant Adverse Events.

Coding Dictionary Evaluation
The NDA safety analyses are based on AE terms that were coded using Medical Dictionary for Regulatory Activities (MedDRA®), version 10.0. Coding the various AE verbatim terms reported by study subjects (for example, "pins and needles" sensation) to specific preferred terms (for example, paresthesia) is an important task that allows for the analysis of AEs occurring during drug development programs. The output of the coding process must be evaluated for results that might hamper AE risk evaluation such as lumping unrelated events under single preferred terms, splitting similar events into multiple terms or coding events to preferred terms so vague that they have limited value. Such occurrences can be present in any NDA, usually with little consequence, but it is important to look for coding inadequacies that could impact the safety assessment.

There were instances of coding inadequacies, especially regarding categorization of application site conditions. I identified instances where similar events were split into different preferred terms. For example, the sponsor split similar clinical events of application site pain to the coded terms: application site pain, application site discomfort, hyperesthesia, and procedural pain. To take into account this coding approach, I conducted additional analyses by pooling preferred terms to assess application site conditions.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The pooled data summarizing the safety experience is obtained from the 2 long-term, open-label, Phase 3 trials (NP101-008 and NP101-009). These trials are identical in study design. The major difference between the two trials is that trial NP101-008 enrolled subjects who were previously enrolled in trial NP101-007 whereas trial NP101-009 enrolled subjects who were predominantly NP101 patch naïve. Presented separately are the safety results for the randomized, double-blind, placebo-controlled, single-treatment, Phase 3 trial (NP101-007) as this trial was markedly different in trial design and exposure to the long term trials.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The average number of monthly NP101 transdermal patch exposures by subjects in the long term, open label Phase 3 clinical trials was less than the exposures agreed upon by the sponsor and the Agency.

At the pre-NDA meeting held with the sponsor on 24 November 2009, the Agency accepted the sponsor's proposal to include at least 300 subjects who would treat their migraines with an average of 3 NP101 transdermal patches per month for 6 months and at least 50 subjects who would treat their migraines with an average of 3 NP101 patches per month for 12 months.

The number of subjects proposed by the sponsor was less than ICH guidelines which recommends data on 300 subjects treated for 6 months and 100 subjects treated for 12 months. Although the number of subjects proposed for acquisition of long term safety data was less than recommended by ICH guidelines, the Agency found the sponsor's proposal acceptable due to the well known safety profile of sumatriptan in other formulations.

The sponsor submitted data on 179 subjects who treated >2 attacks per month for 6 months, and 32 subjects who treated >2 attacks per month for 1 year. Please refer to Table 23 for details. Recall that the sponsor had proposed to include data on at least 300 subjects who would treat their migraines with an average of 3 patches per month for 6 months and at least 50 subjects who would treat their migraines with an average of 3 patches for 12 months. It is unclear from the table provided by the sponsor exactly how many subjects treated an average of 3 migraines per month for 6 and 12 months. Data on average number of patches used per month are grouped as 2.6 to 3.0 patches per month and >3.0. Even if all subjects in the 6 month completers group who treated an average of 2.6 to >3.0 were added together (123 subjects), it is still far less than the 300 subjects proposed by the sponsor. Regardless, the data submitted for long term studies, especially for the 6 month completers, is less than agreed upon. Please refer to Table 23 for details.

Table 23 Summary of Patch Usage in Long Term Safety Trials (NP101-008 and NP101-009)

Parameter	NP101 (N=662)	6 Month Completers (N=319)	12 Month Completers (N=59)
Average Patches per Month			
n	660	319	59
Mean	2.05	2.42	2.45
SD	1.195	1.155	1.080
Median	1.89	2.20	2.25
Min, max	0.1, 6.5	0.6, 6.4	0.8, 5.3
Average Patches per Month			
0 to 1	165	26	5
1.1 to 1.5	92	47	8
1.6 to 2.0	149	67	14
2.1 to 2.5	72	56	9
2.6 to 3.0	72	44	4
> 3.0	110	79	19
Patch Usage			
Patch used to treat Migraine	6718	5462	1460
Rescue Patch	439	363	135
Rescue Med	445	326	95
Rescue Patch and Rescue Med	49	30	7

(Source: Sponsor's submission; Clinical Study Report, module 5.3.5.3.28, Table 14.4.1.1)

Even after accounting for the 120-day safety update data, the average number of monthly exposures is still less than proposed. There were 165 subjects who treated >2 migraine attacks per month for 6 months and 100 subjects who treated >2 migraine attacks per month for 12 months (Table 24). Similar to the initial data, it was unclear from the 12-day safety update data table exactly how many subjects treated an average of 3 migraines per month for 6 and 12 months. The average number of patches used by all 6 month completers was 2.30 and by 12 month completers was 2.47. Overall, the average number of patch exposures in the long term studies is less than the agreement reached with the Agency (Table 24).

Table 24 120-Day Safety Update of Patch Usage in Long Term Safety Trials (NP101-008 and NP101-009)

Parameter	NP101 (N=662)	6 Month Completers (N=338)	12 Month Completers (N=163)
Average Patches per Month			
n	660	338	163
Mean	1.97	2.30	2.47
SD	1.171	1.174	1.070
Median	1.75	2.00	2.33
Min, max	0.1, 6.0	0.5, 6.0	0.8, 6.0
Average Patches per Month			
0 to 1	179	37	10
1.1 to 1.5	100	57	23
1.6 to 2.0	154	79	30
2.1 to 2.5	66	52	33
2.6 to 3.0	62	39	25
> 3.0	99	74	42
Patch Usage			
Patch used to treat Migraine	7946	6821	4211
Rescue Patch	497	422	262
Rescue Med	501	393	264
Rescue Patch and Rescue Med	56	37	15

(Source: Sponsor's submission; CSR: 120-Day Safety Update, module 5.3.5.3.28, Table 14.4.1.1)

7.2.2 Explorations for Dose Response

This is a 505(b)(2) application, based on bioequivalence to the referenced listed drug, Imitrex®, (sumatriptan succinate). No new data exploring a dose response was acquired.

7.2.3 Special Animal and/or In Vitro Testing

The sponsor reported results of animal trials assessing risk of single and repeat dose toxicity studies. These data are examined in detail in section 4.3, Nonclinical Pharmacology / Toxicology.

7.2.4 Routine Clinical Testing

The routine clinical safety testing in the NP101 trials seemed appropriate and capable of identifying major safety signals. The following routine clinical testing was conducted in the Phase 3 clinical trials evaluating NP101 patch exposures in enrolled subjects.

- Adverse events
- Vital signs
- Electrocardiograms (ECGs)
- Physical examinations

- Use of concomitant medications
- Pregnancy testing

7.2.5 Metabolic, Clearance, and Interaction Workup

The sponsor's in vitro and in vivo testing for NP101 was extensively reviewed by the clinical pharmacologists and toxicologists at the FDA. Details of these assessments can be found above in Section 4.4, Clinical Pharmacology Review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Please see Review Section 2.4, where the triptan class safety issues are presented. As noted, the triptans have several areas that have been identified for close monitoring in the trials. The events are:

Drug-Associated Cardiac Events and Fatalities: These have been observed both in the Premarketing Experience and Post-marketing Experience with triptans as detailed in Section 2.4. There were no fatalities in any of the sponsor's trials. ECG findings are presented in Section 7.4.4, Electrocardiograms.

Drug-Associated Cerebrovascular Events and Fatalities: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with oral or subcutaneous triptan, and some have resulted in fatalities. No reported incidences of cerebrovascular events were documented in any of the sponsor's trials.

Other Vasospasm-Related Events: Triptans may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported. Vital Signs were routinely monitored

Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome may occur with triptans, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs).

Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients with and without a history of hypertension.

Concomitant Drug Use: In patients taking MAO-A inhibitors, sumatriptan plasma levels attained after treatment with recommended doses are nearly double those obtained under other conditions.

Use in Women of Childbearing Potential: Pregnancy tests were conducted routinely during the trials. Outcomes of the reported pregnancies in the clinical trials are discussed below in Section 7.6.2 (Human Reproduction and Pregnancy Data).

Hypersensitivity: Hypersensitivity (anaphylaxis/anaphylactoid) reactions were evaluated during the periodic visits and exams.

These events, ischemic heart disease, hepatotoxicity, hypersensitivity, cerebrovascular events, convulsive disorders, visual disturbances, and possible interactions with serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) (serotonergic syndrome) have been identified by the FDA for safety monitoring.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported during the clinical development program of NP101.

7.3.2 Nonfatal Serious Adverse Events

The sponsor defined a serious adverse event (SAE) as any AE that resulted in one or more of the following:

- Death
- Life-threatening Event – The subject was at risk of death at the time of the event. It did not refer to the hypothetical risk of death if the AE was more severe or was to progress.
- Inpatient Hospitalization (admission or prolongation).
- Persistent or Significant Disability/Incapacity – Any AE having an outcome that was associated with a substantial disruption of the ability to carry out normal life functions. This included the inability to work. This was not intended to include transient interruptions of daily activities.

- Congenital Anomaly/Birth Defect – Any structural abnormality in subject offspring that occurred after intrauterine exposure to treatment.

- Other Medically Important Events – Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon medical judgment, they may jeopardize the subject or may require intervention to prevent one of the outcomes listed in (the bullet points) above.

Phase 1 trials
There were no SAEs reported in any of the Phase 1 trials.

Study NP101-007
One SAE, uncontrolled hypertension, was reported. The subject with the SAE was randomized but had not received any treatment.

Long term safety studies (Studies NP101-008 and NP101-009)
Nine SAEs were reported during the long-term studies: atrial fibrillation, supraventricular tachycardia, syncope, ruptured ectopic pregnancy, vertigo, headache, dehydration, nephrolithiasis, and back pain. None of these events were considered by the investigators to be related to study treatment. I have reviewed the narrative for the cases and concur.

SAEs in the Safety Update
The sponsor reported 1 more SAE during the period covered by the Safety Update (safety information on all patient visits through 15 December 2010). The newly reported SAE was for multinodular goiter. The event was determined to be serious but not related to study treatment. I have reviewed the narrative for this case and concur.

7.3.3 Dropouts and/or Discontinuations

There was inadequate information on reasons for treatment discontinuation, especially withdrawal of consent. This was most evident in the long term safety studies. Additionally, in the long terms safety studies, there was a very large number of subjects that discontinued participation. Overall the rate of discontinuation and withdrawal of consent was much higher than in other migraine trials.

Study NP101-007
I have summarized the reasons for discontinuation of subjects in the placebo controlled, randomized, single-patch treatment trial in the table below. Overall, 5% of subjects

discontinued from the trial. Adverse events and problems with the patch were the most common reasons for discontinuation.

The AEs consisted mostly of application site pain. In the NP101 treatment group 4 subjects discontinued because of application site pain and 1 subject discontinued because of application site reaction. In the placebo patch group, 2 subjects had application site pain and 1 subject had blistering of skin over the patch site as well as application site pain.

Seven subjects in the trial discontinued because of problems with their patch. Two of the subjects in the NP101 treatment group had problems with patch adherence and transfer of patch medication pads. The remaining 5 subjects (in both NP101 and placebo groups combined) discontinued because their patch either failed or functioned improperly.

Table 25 Reasons for Discontinuation in Study NP101-007

	Study NP101-007 (Single Patch Treatment)		
	NP101 N (%)	**Placebo N (%)**	**Total N (%)**
Safety Population	234 (100)	235 (100)	469 (100)
Completed study	222 (94.9)	226 (96.2)	448 (95.5)
Discontinued study:	**12 (5.1)**	**9 (3.8)**	**21 (4.5)**
Adverse event	5 (2.1)	3 (1.3)	8 (1.7)
Study patch problem/failure	3 (1.3)	4 (1.7)	7 (1.5)
Lost to follow-up	4 (1.7)	1 (0.4)	5 (1.1)
No qualifying headache	0	1 (0.4)	1 (0.2)

(Source: Sponsor's submission; ISS Table 14.1.1a and Clinical Study Report module 5.3.5.1.3)

Long term safety studies (Studies NP101-008 and NP101-009)

A very large number of subjects discontinued participation in the long term safety studies. Over half of the subjects (55%) in the long term trials discontinued. The most common reason given for discontinuation was withdrawal of consent (20%). The reasons for subject withdrawals were not provided. Please refer to Table 26 for details. Overall, the number of discontinuations and withdrawal of consent reported is much larger than in other migraine trials.

Table 26 Reasons for Discontinuation from Long Term Studies

	Long Term Studies (NP101-008 and NP101-009)		
	NP101-008 N (%)	**NP101-009 N (%)**	**Total N (%)**
Safety Population	183 (100)	479 (100)	662 (100)
6-month completer	76 (41.5)	243 (50.7)	319 (48.2)
12-month completer	51 (27.9)	8 (1.7)	59 (8.9)
Ongoing	0	226 (47.2)	226 (47.2)
Completed study	65 (35.5)	8 (1.7)	73 (11.0)
Discontinued study:	**118 (64.5)**	**245 (51.1)**	**363 (54.8)**
Adverse event	25 (13.7)	60 (12.5)	85 (12.8)
Withdrew consent	52 (28.4)	77 (16.1)	129 (19.5)
Non-compliance	10 (5.5)	47 (9.8)	57 (8.6)
Lost to follow-up	17 (9.3)	22 (4.6)	39 (5.9)
Other	14 (7.7)	39 (8.1)	53 (8.0)

(Source: Sponsor's submission; Clinical Study Report module 5.3.5.3.28, Table 5)

Adverse events leading to discontinuation were predominantly due to patch site conditions. The sponsor reports 13% of subjects discontinued from the long term safety trials due adverse events. Over 90% of the reasons for discontinuation were related to adverse events from the transdermal patch. A listing of the reasons for discontinuation from the long term trials is provided in the sponsor's table below.

Table 27 Summary of Discontinuations from Long Term Trials

MedDRA Preferred Term	Number (%) of Subjects (N=662)
Patch application site conditions	
Application site hypersensitivity	23 (3.5)
Application site pain	21 (3.2)
Application site pruritus	8 (1.2)
Application site discoloration	7 (1.1)
Application site irritation	5 (0.8)
Application site vesicles	4 (0.6)
Application site reaction	3 (0.5)
Application site bruising	2 (0.3)
Application site dryness	2 (0.3)
Application site anaesthesia	1 (0.2)
Application site burn	1 (0.2)
Application site discomfort	1 (0.2)
Application site induration	1 (0.2)
Application site paraesthesia	1 (0.2)
Application site rash	1 (0.2)
Other events	
Depression	3 (0.5)
Nausea	2 (0.3)
Supraventricular tachycardia	1 (0.2)
Diarrhea	1 (0.2)
Herpes zoster	1 (0.2)
Headache	1 (0.2)
Rash maculo-papular	1 (0.2)

(Source: Sponsor's submission; Summary of Clinical Safety 2.7.4, Table 16)

7.3.4 Significant Adverse Events

Significant AEs occurred at site of patch application. The product has significant irritation potential and is sensitizing. Of the 796 subjects in the Phase 3 studies (NP101-007, 008, and 009) who applied at least 1 patch, 43 (5.4%) sustained a severe adverse event.

Adverse events that occurred after activation of the first patch were categorized as treatment emergent. Treatment emergent adverse events were further delineated as to their severity. The severity of a TEAE was defined in the trials as mild, moderate or severe. The sponsor provided the following definitions for the severity of TEAE:

- Mild: "transient and easily tolerated by the subject"
- Moderate: "caused the subject discomfort and interrupted the subject's usual activities"
- Severe: "caused considerable interference with the subject's usual activities and may have been incapacitating or life-threatening"

The table below presents application site TEAE by severity of all subjects in the safety population. Almost half of all subjects (376/796, 47%) in the 3 Phase 3 studies sustained a TEAE. Forty three subjects (5.4%) had a severe TEAE from patch application. Review of the table shows that there were 3 cases of severe skin burns, 15 cases of severe pain, 12 cases of hypersensitivity reactions, and 7 cases of severe pruritus.

Table 28 Summary of TEAE by Severity from Patch Application in Safety Population

System organ class	NP101 (N=796)			
MedDRA 10.0 preferred term, n (%)	Mild	Moderate	Severe	Total
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	202(25.4)	131(16.5)	43(5.4)	376(47.2)
Adverse drug reaction	9(1.1)	2(0.3)	0	11(1.4)
Application site anaesthesia	0	1(0.1)	0	1(0.1)
Application site bruising	16(2.0)	2(0.3)	1(0.1)	19(2.4)
Application site burn	0	2(0.3)	3(0.4)	5(0.6)
Application site discharge	0	0	1(0.1)	1(0.1)
Application site discolouration	29(3.6)	4(0.5)	1(0.1)	34(4.3)
Application site discomfort	4(0.5)	1(0.1)	0	5(0.6)
Application site dryness	31(3.9)	1(0.1)	0	32(4.0)
Application site erosion	0	2(0.3)	0	2(0.3)
Application site erythema	3(0.4)	0	1(0.1)	4(0.5)
Application site excoriation	2(0.3)	0	0	2(0.3)
Application site exfoliation	17(2.1)	1(0.1)	0	18(2.3)
Application site hyperaesthesia	9(1.1)	2(0.3)	1(0.1)	12(1.5)
Application site hypersensitivity	8(1.0)	10(1.3)	12(1.5)	30(3.8)
Application site induration	0	0	1(0.1)	1(0.1)
Application site inflammation	1(0.1)	0	0	1(0.1)
Application site irritation	0	4(0.5)	5(0.6)	9(1.1)
Application site oedema	0	2(0.3)	0	2(0.3)
Application site pain	75(9.4)	81(10.2)	15(1.9)	171(21.5)
Application site papules	2(0.3)	0	0	2(0.3)
Application site paraesthesia	53(6.7)	6(0.8)	2(0.3)	61(7.7)
Application site pruritus	76(9.5)	37(4.6)	7(0.9)	120(15.1)
Application site rash	5(0.6)	1(0.1)	0	6(0.8)
Application site reaction	42(5.3)	8(1.0)	1(0.1)	51(6.4)
Application site scar	1(0.1)	0	0	1(0.1)
Application site swelling	5(0.6)	3(0.4)	0	8(1.0)
Application site urticaria	1(0.1)	1(0.1)	0	2(0.3)
Application site vesicles	6(0.8)	10(1.3)	1(0.1)	17(2.1)
Application site warmth	16(2.0)	5(0.6)	0	21(2.6)

(Source: Adapted from sponsor's submission; Summary of Clinical Safety: 4-Month Safety Update, Labeling Summary #1 in Appendix B)

The Agency's Division of Dermatology was consulted to review the sensitization and irritation potential of NP101 in the long term studies. The review was conducted by Dr. Snezana Trajkovic and is presented as an Addendum in the Appendix. Dr. Trajkovic's report concludes that the product, NP101, "has significant irritation potential and is sensitizing". Since the long term studies were open label and no placebo containing patches were evaluated, Dr. Trajkovic states that "it is not possible to conclude if device or drug component of this combination product is responsible for irritation and sensitization". Please refer to Dr. Trajkovic's review for details of the skin irritation assessments and sensitization potential of NP101. Additionally, an overview of delayed hypersensitivity /allergic contact dermatitis findings in the long term safety studies is presented below.

Delayed Hypersensitivity / Allergic Contact Dermatitis (ACD)
Application of topical products can cause delayed hypersensitivity reactions (also referred to as allergic contact dermatitis, ACD). The development of topical sensitivity to sumatriptan was evaluated in the long term safety studies. Overall, there was a 7.3% rate (44/606) of putative cases of ACD in the combined long term safety studies. There were no cases of systemic hypersensitivity or record of any subject requiring emergency care for hypersensitivity reaction reported in the long term studies.

To evaluate for ACD, all subjects were required to complete a skin self-examination evaluation upon removal of the patch, and again at 6, 12, and 24 hours post patch removal. The following five-point skin assessment scale was used by subjects: 0 = no redness; 1 = minimal skin redness; 2 = moderate skin redness with sharp borders; 3 = intense skin redness with or without swelling; and 4 = intense skin redness with blisterfs or broken skin.

Subjects skin-examination were also evaluated by a medical monitor within 24 hours if subjects documented a score of 3 or 4 on the five-point scale, or developed worsening skin assessment score after a period of improvement. A similar scale as the subject five-point self-skin examination scale was used by the study investigator. The investigator skin irritation score is presented in Table 6.

After completing the study, all subjects had their records reviewed for ACD by a medical safety review team. The cases identified by the safety review team as ACD as well as those reported in the database as ACD during the trial were assessed by Dr. Howard Maibach, a dermatology ACD specialist, who was consulted by the sponsor.

Dr. Maibach identified 44 cases (44/606) of either "probable" or "possible" ACD cases in the long term safety studies. Cases were classified as "possible" when the evidence for a clinical diagnosis of ACD was not strong but it could not be ruled out. When the evidence was strong for a clinical diagnosis of ACD, it was classified as "probable".

Of the 44 cases identified by Dr. Maibach, 18 were classified as probable ACD and 26 were considered as possible ACD. Combining probable and possible cases, ACD occurred at a rate of 7.3% in the long term studies.

Recovery from ACD varied widely in subjects. It took an average of 26 days (ranging from 4 days to 101 days) for subjects with a skin irritation score of 4 (intense erythema with edema and blistering/erosion) to be reduced to 0 (no erythema).

Subjects identified as having putative case of ACD had the option for allergy testing to sumatriptan and NP101 medication pad. Only 4 subjects agreed to the allergy testing. All 4 subjects tested negative.

120-Day Safety Update
An additional 4 cases of ACD were detected in the 120-day safety update, making a total of 48 cases (48/607) of ACD in the long term safety studies. With the additional cases in the safety update, the rate of ACD in the long term studies increases to 7.9%.

Burns and discoloration of skin
Review of TEAEs of the safety population including the 120-Day Safety Update revealed 3 cases of severe skin burns and 2 cases of moderate skin burns at the patch application site. There were also 1 case of severe skin discoloration and 4 cases of moderate skin discoloration at the patch application site.

Specific details about the individual cases of skin burns and discoloration were difficult to ascertain from the submission. The sponsor did not discuss the specific cases of skin burns and discoloration as a distinct group. Rather, these cases were intermingled as part of a group of subjects that either discontinued from the trials due to an AE or were presented as cases of AEs that occurred from improper patch application.

Review of AEs by study visit month revealed the occurrences of skin burns were documented on study months: 1, 2, 9, and 10. Occurrence of moderate and severe discolorations was difficult to distinguish by study month as all cases (mild, moderate and severe) were presented together.

The sponsor states that intense erythema and blistering can occur if the medication pads are not transferred properly to completely cover the 2 electrodes on the E-Patch. There were 4 cases of intense erythema and blistering of skin from improper patch application that was discussed in the original submission by the sponsor.

I reviewed the submission for details and narratives regarding skin burns and discoloration. Overall, there was inadequate information specific to these significant AEs. Below, I present the sponsor's narratives of 4 cases selected from the submission which highlight the significant AE of burns and discoloration sustained from patch application.

- **(Study NP101-007) Subject 100-1203**, subject was in placebo group: 36-year-old white female, with past medical history significant for concussion, depression, acid reflux, deep vein thrombosis, cholecystitis and cholecystectomy, and cellulitis inadvertently applied placebo patch without the medication pads. The patch was activated and left in place for four hours. The subject felt 'shock-like' sensations for one hour. The LED light was on the entire time. The subject noted blisters (location unknown) after removing the patch (subject skin irritation score = 4). The original skin findings were limited to the area under where the medication pads were supposed to have been located. On one side there was grade 4 erythema and edema with two small blisters (about 1 mm) centrally located. The other side had grade 3 erythema and edema although there was a V-shaped area that was described as deep dermal involvement / partial thickness / blister. There were no other skin reactions outside of these two areas. The Investigator skin irritation score = 4. The lesions were described by consultant plastic surgeon as superficial burn with localized area full thickness. The subject was treated with Keflex® and topical Bacitracin®. The subject's lesions were completely healed without a residual mark at the eight week Follow-up Visit.

- **(Study NP101-007) Subject 127-1197,** a 26-year-old white female, with no significant medical history except for allergies towards sulfa drugs and penicillin, inadvertently applied NP101 patch without the medication pads. Approximately 25-30 minutes after patch activation, the subject developed mild pain which was initially reported to last through the end of the four-hour patch application time. The LED light was on for entire time. At the time of patch removal (after four hours), the subject noted redness and blistering (subject skin irritation score = 4). The subject was seen by the Principal Investigator approximately 48 hours after patch removal. The Principal Investigator described a 3.5 x 2 cm crescent-shaped area with moderate erythema / vesiculation under one electrode area and a second area 1.5 x 3 cm of minimal erythema under the second electrode. Also two areas of skin erosion centrally located (1.0 cm, 0.5 cm) under the first electrode with minimal erythema (which were scabbed over) were noted. The Investigator skin irritation score = 4. Upon follow-up, the subject reported that pain had stopped three days after patch application. The subject did not come back for further follow-up despite multiple follow up attempts by the investigative site. Three months after patch application, the subject provided information to the Principal Investigator over the phone that she had healed completely. During a nonscheduled out-of-office encounter 4.5 months after the event, the Principal Investigator observed and reported a slightly raised keloid of 2 x 1 cm at the application site and some discoloration of the skin in that area. Follow-up and specialist referrals were declined by subject who said that she was not concerned about the appearance and felt fine.

- **(Study NP101-007) Subject 125-1275**, an 18-year-old Asian female, with no significant medical history except for irregular menstrual cycle, applied NP101 patch and had no issue with medication pad transfer. The patch was worn for four hours. The subject's migraine headache pain went from moderate to no pain at four hours. The subject noted tingling / burning at patch site at onset of patch activation but no pain. After removing the patch, the subject reported pain / burning and small blisters at application site. The investigator reported erythema (intense and over both medication pad areas) and one open 5 mm blister under one medication pad site only. Small pimple-like lesions under the anode and cathode sides were described. The subject noticed leaking of patch. The Investigator skin irritation score = 4. No specific treatment given. In follow-up, the subject skin irritation score returned to 0 approximately two weeks after initial event. The subject was seen by the Principal Investigator two and a half weeks after the event; the skin irritation score = 0 (with minimal residual mark in area of previously noted blister). The subject was discharged from study without any further follow-up / treatment.

- **(Study NP101-009) Subject 134-2221,** a 28-year-old white female. Subject applied 2 patches in the study. The second patch application was 2 hours after the first one and was unremarkable with skin recovery to score "0" within 6 hours. Post patch application 1, the AE "3rd degree skin burn right thigh at patch site" of severe severity was recorded. It was established that medication pad did not fully cover the patch electrode. The crescent shaped burn of 1.2 centimeters mirrored the uncovered electrode area. Cleaning the area with soap and water and application of Neosporin ointment twice per day was recommended by investigator. The AE lasted eighty days and was the reason for discontinuation from the study. After eighty days post patch application, the AE "skin discoloration at patch site" was recorded and is still ongoing. Subject has had two consultations with dermatologist and one with a plastic surgeon and her current decision is not to undergo cosmetic repair for the discoloration.

  Subject 134-2221, 120 Day Safety Update:
  The adverse event of 'skin discoloration at patch site' which started on March 1 2010, approximately 3 months after the last study patch was applied (following resolution of a third degree burn at patch site), was still reported as on-going as of January 21 2011.

7.3.5 Submission Specific Primary Safety Concerns

The skin irritation potential of the product is of concern. Significant as well as common adverse events at the application site with use of the transdermal patch are discussed in detail in Sections 7.3.4 (Significant Adverse Events) and 7.4.1 (Common Adverse Events).

In assessing dermal AEs related to patch use, it was unclear from the sponsor's submission, the minimal time interval between 2 applications of the patch at the same site. Subjects were instructed not to apply more than 2 patches in a 24-hour period. They were also instructed not to apply a patch to a previous application site until the site remained erythema free for 72 hours.

The sponsor did conduct a study (NP101-014) evaluating cumulative skin irritation potential of the transdermal patch in healthy volunteers. The trial was terminated with the first 10 subjects because to adverse events related to application site irritation. Details of the study are provided in Section 7.4.5 (Special Safety Studies/Clinical Trials).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study NP101-007
The sponsor reported that 50% of all subjects in the NP101 treatment group (117/234) and 44% of the placebo group (103/225) in efficacy study (NP101-007) experienced at least one TEAE. The sponsor's summary of TEAE as reported by 2 or more subjects in the efficacy study are presented in Table 29.

Table 29 Summary of TEAE Reported by 2 or More Subjects in Study NP101-007

	Number (%) of Subjects Reporting Event			
	NP101 (N=234)		Placebo (N=235)	
Adverse Event, Preferred term	All	Related	All	Related
Total subjects with at least one treatment-emergent AE	117 (50.0)	114 (48.7)	103 (43.8)	100 (42.6)
Application site pain	54 (23.1)	54 (23.1)	34 (14.5)	34 (14.5)
Application site paraesthesia	28 (12.0)	28 (12.0)	44 (18.7)	44 (18.7)
Application site pruritus	18 (7.7)	18 (7.7)	16 (6.8)	16 (6.8)
Application site reaction	16 (6.8)	16 (6.8)	13 (5.5)	13 (15.5)
Application site warmth	9 (3.8)	9 (3.8)	4 (1.7)	4 (1.7)
Application site discoloration	5 (2.1)	5 (2.1)	3 (1.3)	3 (1.3)
Adverse drug reaction	4 (1.7)	4 (1.7)	0	0
Nausea	3 (1.3)	3 (1.3)	0	0
Application site bruising	2 (0.9)	2 (0.9)	0	0
Application site dryness	2 (0.9)	2 (0.9)	0	0
Dizziness	2 (0.9)	2 (0.9)	1 (0.4)	1 (0.4)
Fatigue	2 (0.9)	2 (0.9)	0	0
Somnolence	2 (0.9)	2 (0.9)	3 (1.3)	3 (1.3)
Dysgeusia	1 (0.4)	1 (0.4)	2 (0.9)	2 (0.9)
Abdominal pain upper	0	0	2 (0.9)	1 (0.4)
Pharyngolaryngeal pain	0	0	2 (0.9)	0

(Source: Summary of Clinical Safety, module 2.7.4, Table 9)

Most TEAE were classified as mild in severity. In the NP101 treatment group 31% of subjects (72/234) had AEs that were mild. Moderate severity AEs constituted 16% of subjects (38/234) and severe events occurred in 3% of subjects (7/234) in the NP101 treatment group. The placebo group had 34% of subjects (79/235) with AEs that were classified as mild. Moderate events occurred in 9% of subjects (20/235) and severe AEs occurred in 1% of subjects (2/235) in the placebo group.

By far, the predominant AEs were application site conditions. Adverse events other than application site conditions occurred at a low rate: 6% in the NP101 group and 4% in the placebo group.

When analyzing application site events, I detected instances of coding inadequacies. There were instances where similar events were split into different preferred terms. To take into account this coding approach, I conducted subset analyses of all application site events reported by 2 or more subjects. I grouped the application site events into 3

major categories: application site pain, application site reaction, and application site pruritus.

More application site pain was reported by 2 or more subjects in the NP101 treatment group (23%) than reported in the placebo group (15%). There was a relatively equal distribution of events reported by both groups for application site reaction and pruritus. Application site reactions constituted 26% of events reported by 2 or more subjects in the NP101 group compared to 27% reported in the placebo group. Likewise, 8% of application site events in the NP101 group were from pruritus whereas in the placebo group, it was 7% of reported application site events. Please refer to Table 30 for details.

Table 30 Application Site TEAE (Reported by 2 or More Subjects) in Study NP101-007

AE Preferred Term	NP101 Number (%) of Events	Placebo Number (%) of Events
Application Site Reaction Reaction Paraesthesia Dryness Discoloration Bruising Warmth	62 (26%)	64 (27%)
Application Site Pain	54 (23%)	34 (15%)
Application Site Pruritus	18 (8%)	16 (7%)

(Source: Clinical Study Report, module 5.3.5.1.3, Tables 28, 14.3.1.2, and 14.3.2.)

Triptan sensation

The sponsor reported that all TEAE were reviewed for triptan sensation. In the NDA, triptan sensation was also referred to as “adverse drug reaction”. Triptan sensation was defined as “pain and pressure sensations, including chest pain/tightness/pressure and/or heaviness, and pain/tightness/pressure of the neck, throat, or jaw; and atypical sensations, including paresthesia and sensations of warmth/cold.”

Overall, 9 subjects were determined to have a triptan sensation. Of the 9 subjects, 8 (3%) were in the NP101 group. Interestingly, 1 subject that was deemed to have a triptan sensation was in the placebo group. The sponsor reported that all the triptan sensations were mild (with the exception of “cold sensation head” that was moderate in intensity). A summary of the types of AEs classified as triptan sensation is presented in the sponsors table below.

Table 31 Summary of Subjects with AEs Classified as Triptan Sensations

Total Subjects (ITT)	Verbatim Term	NP101 N=234 (%)	Placebo N=235 (%)
Atypical Sensations		**4 (1.7)**	**0 (0)**
Paraesthesias (all types)	nasal burning sensation	1	0
Sensation (warm / cold)	cold sensation head hot feeling throughout body intermittent facial flushing	3	0
Pain and Other Pressure Sensations		**4 (1.7)**	**1 (0.4)**
Chest-pain, tightness, pressure, heaviness	chest tightness	1	0
Neck / Throat / Jaw – pain, tightness, pressure, heaviness	throat constriction neck tightness neck pain	3	0
Pain-location specified	stomach pain	0	1
Pain-location not specified		0	0
Other-tightness, pressure, heaviness (location specified)		0	0
Other-tightness, pressure, heaviness (location not specified)		0	0

(Source: Sponsor's submission; Clinical Study Report, module 5.3.5.1.3, Tables 29)

Long term safety studies (Studies NP101-008 and NP101-009)

The sponsor reported that 53% (348/662) of subjects in the long term trials experienced at least one TEAE. The sponsor's summary table of TEAE reported by >1% of subjects in the long term safety studies is presented in Table 32. Most TEAE were classified as mild or moderate in intensity. Overall, 23% of subjects (151/662) had AEs that were mild, 21% (140/662) experienced moderate AEs, and severe AEs occurred in 9% of subjects (57/662).

Table 32 Summary of TEAE Reported by >1 Subjects in the Long Term Safety Trials

System Organ Class	Number (%) of Subjects (N=662)	
MedDRA Preferred Term	All AEs	Treatment-related AEs
Subjects with at least one TEAE	348 (52.6)	280 (42.3)
Gastrointestinal disorders		
Nausea	10 (1.5)	8 (1.2)
General disorders and administration site conditions		
Application site bruising	16 (2.4)	16 (2.4)
Application site discoloration	26 (3.9)	26 (3.9)
Application site dryness	29 (4.4)	29 (4.4)
Application site exfoliation	16 (2.4)	16 (2.4)
Application site hyperaesthesia	11 (1.7)	11 (1.7)
Application site hypersensitivity	28 (4.2)	28 (4.2)
Application site irritation	8 (1.2)	8 (1.2)
Application site pain	117 (17.7)	117 (17.7)
Application site paraesthesia	34 (5.1)	34 (5.1)
Application site pruritus	101 (15.3)	101 (15.3)
Application site reaction	38 (5.7)	38 (5.7)
Application site swelling	7 (1.1)	7 (1.1)
Application site vesicles	16 (2.4)	16 (2.4)
Application site warmth	12 (1.8)	12 (1.8)
Infections and infestations		
Nasopharyngitis	13 (2.0)	0
Sinusitis	8 (1.2)	0
Upper respiratory tract infection	23 (3.5)	0

(Source: Sponsor's submission; Summary of Clinical Safety, module 2.7.4 Table 10)

The predominant AEs reported by at >1% of subjects were applications site conditions. Adverse events other than application site conditions (reported by at least 2% of subjects) occurred at a low rate (9%). A summary of the types and distribution of TEAE is presented in Table 33.

Table 33 TEAE Reported by >1% of Subjects Treated with NP101 in the Long Term Safety Trials

MedDRA Preferred Term	TEAEs Number (%) of Events
Application Site Conditions Reaction Pain Pruritus Hypersensitivity	459 (69%)
Infections Upper respiratory tract infection Nasopharyngitis Sinusitis	44 (7%)
Gastrointestinal Disorders Nausea	10 (2%)

(Source: Sponsor's submission; Summary of Clinical Safety, module 5.3.5.3, Tables 14.6.1 and 14.7.1)

When analyzing application site events, I detected instances of coding inadequacies. There were instances where similar events were split into different preferred terms. For example, the sponsor split similar clinical events of application site pain to the coded terms: application site pain and application site hyperesthesia. To take into account this coding approach, I conducted subset analyses of all application site events reported by >1% of subjects. I grouped the application site events into 4 major categories: application site reaction, application site pain, application site pruritus, and hypersensitivity. Please refer to Table 34 for details.

Approximately 1/3 of application site conditions reported by >1% of subjects were application site reactions (such as paresthesia, exfoliation, bruising, and formation of vesicles at the patch application site). Almost 20% of all application site conditions were due to pain at the NP101 application site. Another 15% of application site events were pruritus and 4% were due to hypersensitivity reactions.

Table 34 Application Site Conditions Experienced by >1% of Subjects Treated with NP101 in the Long Term Safety Trials

MedDRA Preferred Term	TEAEs Number (%) of Events
Application Site Reaction Reaction Paraesthesia Dryness Exfoliation Discoloration Bruising Vesicles Swelling Warmth	202 (31%)
Application Site Pain Pain Hyperaesthesia	128 (19%)
Application Site Pruritus	101 (15%)
Application Site Hypersensitivity	28 (4%)

(Source: Sponsor's submission; ISS module 2.1.1.1.3, Tables 10, 14.3.1.2, and 14.3.2)

The sponsor reported that all TEAE were reviewed for triptan sensation in the long term trials. Parameters used for determination of triptan sensation included: subject history, physical examination, the AE and its onset relative to application of study patch, and the duration of AE. Overall, 5 subjects (2%) in the combined long term trials were determined to have a triptan sensation. The AEs of triptan sensation were: "feeling cold and shaky", "tingling at back of head", "oral tingling", "dry burning sensation in the nasal passages", and "chest pain". All were mild in intensity, except for "feeling cold and shaky" which was of moderate intensity.

Triptan sensation

The incidence of triptan sensation events (also referred to as adverse drug reaction I the submission) in the combined long term safety studies was very low. There were a total of 5 triptan sensation events (5/662, 0.8%). Four of these events were classified as mild in severity and 1 as moderate severity. No cases were reported as severe.

Skin irritation assessment

As discussed above, the predominant AEs associated with NP101 were application site conditions. Skin irritation assessments were conducted by subjects at specified times from removal of NP101 patch to resolution of skin condition. Subjects who reported a skin irritation score of $\geq$1 performed daily skin examinations and had scheduled follow-

up evaluations by the investigator until resolution of condition and return of skin irritation score to 0.

In study NP101-007, subjects assessed patch site for AEs at 4, 6, 12, and 24 hours post NP101 patch activation and daily until resolution of erythema. Upon patch removal (4 hours post patch activation) 88% (199/226) of the NP101 group reported having an erythema score of ≥1. In the placebo treatment group, 70% of subjects reported having skin assessment score of ≥1 upon removal of patch (4 hours post patch application). By 24 hours, almost 70% of the NP101 treatment group and 30% of the placebo group had erythema scores of ≥1. The mean time to resolution of erythema for NP101 treatment group was 10 days. In the placebo group, the mean time to resolution of erythema was 6 days.

In the long term safety studies, subjects recorded skin assessment scores at 4, 6, 12, and 24 hours after patch activation as well as daily until resolution of skin erythema. Upon patch removal (4 hours post patch activation) 83% (1284/7378) of subjects reported having an erythema score of ≥1. By 24 hours, 47% (3376/7259) of subjects had erythema scores of ≥1. A summary of subject skin assessment by time point (within 24 hours after patch activation) is presented in Table 35.

Table 35 Summary of Skin Assessment by Time Point after Patch Activation in the Long Term Safety Trials

	Time Point Post Patch Application (N=662)			
Skin Assessment Scores	**4 Hours**	**6 Hours**	**12 Hours**	**24 Hours**
Number of patches scored	7378	7457	7340	7259
Distribution, n (%)[a]				
No redness	1284 (17.4)	1862 (25.0)	2601 (35.4)	3883 (53.5)
Minimal redness	2139 (29.0)	2169 (29.1)	2210 (30.1)	1521 (21.0)
Moderate redness	3510 (47.6)	3067 (41.1)	2269 (30.9)	1658 (22.8)
Intense redness with or without swelling	415 (5.6)	333 (4.5)	232 (3.2)	158 (2.2)
Intense redness with blisters or broken skin	30 (0.4)	26 (0.3)	28 (0.4)	39 (0.5)
Missing[b]	10	9	10	12
Mean (SD)	1.4 (0.85)	1.3 (0.90)	1.0 (0.91)	0.8 (0.92)
Median	2.0	1.0	1.0	0.0
Minimum, Maximum	0, 4	0, 4	0, 4	0, 4

[a] The denominator is the total number of patches with a score at the respective time point.
[b] Missing is not included in the denominator.
(Source: Sponsor's submission; Summary of Clinical Safety, module 2.7.4, Table 20)

Skin irritation scores at 24 hours post patch activation were compiled for each study month in the long term trials (Table 36). There was no increase in skin irritation score over progressive months of patch application. Every month in the long term trials more than 40% subjects reported skin irritation scores of ≥1. Resolution of erythema ranged from 0.2 days to 164 days (mean of 3 days).

Table 36 Summary of Skin Assessment by Time Point at 24 Hours after Patch Activation by Study Month in the Long Term Safety Trials

	Subject Skin Irritation Scores at 24 Hours after Patch Activation (N=662)											
	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Number scored	2234	983	814	680	690	506	370	330	245	153	160	92
Distribution, %[a]												
Score = 0	49.0	54.6	56.6	58.7	58.4	52.0	57.8	52.7	56.3	49.7	46.3	51.1
Score =1	26.5	19.6	18.4	15.7	17.2	20.0	14.3	23.3	17.1	22.2	21.3	20.7
Score = 2	21.8	21.7	21.6	22.2	21.4	26.3	26.2	22.4	25.3	27.5	31.3	28.3
Score = 3	2.3	3.1	2.7	2.1	2.8	1.4	1.4	1.5	1.2	0.7	0.6	0
Score = 4	0.4	1.0	0.6	1.3	0.1	0.4	0.3	0	0	0	0.6	0
Mean	0.8	0.8	0.7	0.7	0.7	0.8	0.7	0.7	0.7	0.8	0.9	0.8
SD	0.89	0.96	0.93	0.96	0.91	0.91	0.92	0.86	0.89	0.87	0.92	0.87
Median	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	1.0	0.0
Min, Max	0, 4	0, 4	0, 4	0, 4	0, 4	0, 4	0, 4	0, 3	0, 3	0, 3	0, 4	0, 2

[a] Percentage based on the total number of patches with a 24-hour post patch activation score at the respective study month.
0 = no redness; 1 = minimal redness; 2 = moderate redness; 3 = intense redness with or without swelling; 4 = intense redness with blisters or broken skin; SD = standard deviation.

[a] Percentage based on the total number of patches with a 24-hour post patch activation score at the respective study month.
0 = no redness; 1 = minimal redness; 2 = moderate redness; 3 = intense redness with or without swelling; 4 = intense redness with blisters or broken skin; SD = standard deviation.

(Source: Sponsor's submission; Summary of Clinical Safety, module 2.7.4, Table 21)

7.4.2 Laboratory Findings

Clinical laboratory testing was conducted only at screening visit to determine eligibility into the Phase 3 trials. Urine pregnancy tests were obtained in female subjects of childbearing potential at each scheduled visit in all the Phase 3 trials. Results of the pregnancy tests are discussed in detail in Section 7.6.2, Human Reproduction and Pregnancy Data.

7.4.3 Vital Signs

Vital signs evaluated as part of the safety monitoring during the clinical trials included blood pressure, heart rate, respiratory rate, and temperature. The sponsor reports no clinically significant vital signs shifts in the Phase 1 clinical trials and no trends for

changes in vital signs over time in the long term Phase 3 trials. There were no adverse events reported for vital signs in any of the clinical trials. I reviewed the data and concur. Further information regarding vital signs for the Phase 3 trials are provided below.

Study NP101-007
Vital signs were obtained at screening and randomization visits only. No clinically significant changes in vital signs were detected in the trial.

Long Term Safety Studies: NP101-008 and NP101-009
Vital signs were taken at enrollment and at all scheduled visits (months 1, 2, 3, 6, 9, and 12 or final visit). Clinically noteworthy changes are presented in the sponsor's table below.

Table 37 Summary of Clinically Significant Vital Signs Changes in Trials NP101-008 and NP101-009

Parameter	n/n (%)[a]	
Criteria	NP101 (N=183)	NP101 (N=479)
Subjects with at least one abnormality	7/181	12/473[b]
Systolic blood pressure		
≤90 mm Hg and decrease ≥20 mm Hg	5/181 (2.8)	6/473 (1.3)
≥180 mm Hg and increase ≥20 mm Hg	1/181 (0.6)	0/473
Diastolic blood pressure		
≤50 mm Hg and decrease of ≥15 mm Hg	0/181	0/473
≥105 mm Hg and increase of ≥15 mm Hg	0/181	2/473 (0.4)
Heart rate		
≤50 beats/min and decrease of ≥15 beats/min	1/181 (0.6)	5/473 (1.1)
≥120 beats/min and increase of ≥15 beats/min	0/181	0/473
Temperature		
>38.3°C and change of ≥1.1°C	0/179	0/473

[a] The denominator for calculating the percentage of subjects with abnormality is the number of subjects with a baseline and post-baseline value for each parameter.
[b] One subject had two vital sign measurements that met the criteria for potential clinical significance.

(Source: Sponsor's submission; Clinical Study Report, module 5.3.5.3.28, Table 19)

Close to 3% of subjects in the long term trials had a significant change in a vital sign parameter. Most subjects had a change in just one vital sign parameter. Overall, there

were no apparent trends for changes in vital signs over time and no reported adverse events related to vital signs in the long term Phase 3 trials.

7.4.4 Electrocardiograms (ECGs)

12-lead resting ECGs were obtained on subjects in the Phase 3 trials. ECGs were classified as normal, abnormal/not clinically significant, or abnormal/clinically significant. Approximately 34% of baseline ECGs was determined to be abnormal/not clinically significant. Two subjects in the long term safety trials had ECG changes during the trials. One subject had a clinically significant change in their ECG that was deemed to be an adverse event that was possibly related to study drug. Another subject had an SAE with ECG changes that was determined by the investigator not to be related to study drug. Details of these two subjects are provided below.

Study NP101-007
ECGs were obtained at screening and randomization visits only. No clinically significant changes ECG were noted in the trial.

Long Term Safety Studies: NP101-008 and NP101-009
ECGs were obtained at enrollment, month 6, and month 12 (or final visit). Two subjects had ECG changes during the trials. The following is the sponsor's report of the ECG findings:

- Subject 129-1508 (Study NP101-008) had a normal ECG at baseline and ECGs at Month 6 and 12 that were interpreted as abnormal/clinically significant. This subject was a 22-year-old female with no relevant medical history who was receiving diphenhydramine and fexofenadine for seasonal allergies, azelastine for deviated septum, Cilest® (birth control), and Excedrin® Migraine. On Day 165 (Month 6 Visit), ECG findings were "anterior ST change, isolated PVCs; increased QTc, sinus bradycardia". A repeat ECG performed 5 days later was noted as "abnormal, not clinically significant finding: non-specific ST-T change & slight increased QTc". On Day 332 (Month 12 Visit), ECG findings were "trigeminy; slight increased QTc." Repeat ECG performed 5 days later showed "sinus arrhythmia vs. atrial ectopy: PVCs & questionable clinical significance." The ECG findings on Day 165 were reported as an adverse event (electrocardiogram abnormal) of mild severity and considered possibly related to NP101. The subject had a subsequent follow-up with a cardiology specialist who recommended no therapy and a follow-up in 6 months.

- Subject 129-1508 (Study NP101-009) is a 54-year-old white female with history of hypertension, hypercholesterolemia and seasonal allergies. Subject applied 5 patches over 57 days. The maximum skin irritation score recorded following any patch application was "0". Subject was admitted to the hospital after two days of

abdominal discomfort that intensified with intermittent nausea, palpitations, chest pain and diaphoresis. The ECG upon admission showed atrial fibrillation. Cardizem CD 180 mg po daily and Aspirin 81 mg po daily were prescribed in addition to the Lisinopril 20mg po daily the subject was already on. The SAE recovery was in one day. The SAE was deemed by investigator not related to the study drug. The AE "depression" of mild severity was recorded on the same day of hospitalization. The AE is ongoing and was the reason for discontinuation from the study. The AE was deemed by investigator not to be related to the study drug. Antidepressant medication, Citalopram 20 mg po daily, contraindicated per study protocol, was started for the treatment of the AE.

7.4.5 Special Safety Studies/Clinical Trials

Study NP101-014

The sponsor evaluated cumulative skin irritation potential of the transdermal patch in healthy volunteers (Study NP101-014). This was a randomized, placebo-controlled repeat patch application study comparing NP101 patch to placebo patch. Subjects were to apply and activate one NP101 patch to a designated area of one arm and a placebo patch to a designated area on the other arm. Patches were to be left in place for 23 hours. Subjects were to apply the 2 patches (NP101 and placebo) on the same designated area daily for 21 days.

Enrollment was planned for up to 30 subjects. The trial was designed to enroll 10 subjects at a time. Data was to be reviewed before the next 10 subjects were enrolled. Skin irritation scores, patch adherence, and PK of sumatriptan were evaluated.

The trial was terminated with the first 10 subjects because to adverse events related to application site irritation. All 10 subjects were discontinued from the trial due to development of intense erythema with edema and blistering/erosions within 5 to 7 days of daily patch application. This was a skin irritation assessment score of 4 out 4 in all subjects.

Severe erythema was observed in all the subjects after 4 to 6 days of patch application. The sponsor reports that by day 5, a score 4 in the skin irritation assessment score (intense erythema with edema and blistering/erosions) was reported by 4 subjects. By day 6 there were 3 more subjects who developed skin assessment score of 4; and by day 7, the remaining 3 subjects (10 out of 10) had skin assessment score of 4.

Application site AEs in relation to NP101 or placebo patch were reported as follows: 6 subjects had AEs to the NP101 application site arm, 3 subjects had application site AEs on both arms where patch was applied, and 1 subject reported AE on placebo patch site arm. It took from 21 to 38 days for resolution of skin erythema.

7.4.6 Immunogenicity

No investigations of immunogenicity were submitted for this NDA.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

All clinical trials in the NDA used only the single delivered dose of 6.5 mg sumatriptan, so there were no analyses of adverse events vis-à-vis dosing.

7.5.2 Time Dependency for Adverse Events

Discussion and safety findings of time dependency for adverse events can be found in section 7.4.1 above (under the subsection of Dermatology consultation and skin irritation assessment).

7.5.3 Drug/Product-Demographic Interactions

Treatment emergent adverse events were analyzed by subgroups based on race, age, and BMI for all Phase 3 trials. Summary of subgroup analysis of TEAEs based on gender was presented by the sponsor for the long term trials but not for the single treatment, placebo controlled, double blind trial, NP101-007.

There were no notable differences in TEAEs in the various subgroups analyzed for trial NP101-007 (data not presented in this review). Data for TEAEs by subgroups for the long term safety trials is presented in their respective sections below. As with TEAEs related to NP101 in general, the most common TEAEs in all subgroups analyzed were application site conditions. Respiratory tract infections were the next most commonly occurring condition.

Race
Distribution of TEAEs by race indicated that white subjects had more incidences of application site conditions than non-white subjects (Table 38 Treatment Emergent AEs Based on Race in $\geq$2% of Subjects in Trials NP101-008 and NP101-009). White subjects also had worse skin erythema scores post NP101 patch application than non-white subjects. Resolution of application site erythema was longer in white subjects than in non-white subjects.

Table 38 Treatment Emergent AEs Based on Race in ≥2% of Subjects in Trials NP101-008 and NP101-009

MedDRA Preferred Term	White (N=551) # of subjects (%)	Non-white (N=111) # of subjects (%)
Application site reactions (bruising, discoloration, dryness, exfoliation, paresthesia, reaction, or vesicles)	151 (27.3)	24 (21.6)
Application site pain	103 (18.7)	14 (12.6)
Application site pruritus	88 (16.0)	13 (11.7)
Application site hypersensitivity	26 (4.7)	2 (1.8)
Respiratory tract infections	28 (5.0)	8 (7.2)

(Source: Sponsor's submission; Clinical Study Report, module 5.3.5.3, Tables 14.6.4 and 14.6.5)

Gender

Female subjects had more adverse application site conditions than male subjects (Table 39 Treatment Emergent AEs Based on Gender in ≥2% of Subjects in Trials NP101-008 and NP101-009). The disparity was most pronounced for application site hypersensitivity with 5% of women experiencing hypersensitivity reaction compared to 0.8% of men. There were no appreciable differences in skin erythema scores post NP101 patch application or in the time to resolution of erythema between female and male subjects.

Table 39 Treatment Emergent AEs Based on Gender in ≥2% of Subjects in Trials NP101-008 and NP101-009

	Number (%) of Subjects Reporting Event	
MedDRA Preferred Term	**Female, N=544**	**Male, N=118**
Application site reactions (bruising, discoloration, dryness, exfoliation, paresthesia, reaction, vesicles, or warmth)	167 (30.7)	20 (16.7)
Application site pain	102 (18.8)	15 (12.7)
Application site pruritus	89 (16.4)	12 (10.2)
Application site hypersensitivity	27 (5.0)	1 (0.8)
Respiratory tract infections	28 (5.2)	8 (6.7)

(Source: Sponsor's submission; Clinical Study Report, module 5.3.5.3, Tables 14.6.6 and 14.6.7)

Age

There were no notable differences in TEAE incidence of application site conditions with regards to age (Table 40 Treatment Emergent AEs Based on Age in ≥2% of Subjects in Trials NP101-008 and NP101-009). Younger subjects (less than the median age of 43), however, had greater reported incidences of respiratory tract infections. The sponsor reported that subgroup analyses of subject skin assessment scores did not indicate any difference between age groups with regards to skin erythema scores post NP101 patch application or in the time of resolution of erythema.

Table 40 Treatment Emergent AEs Based on Age in ≥2% of Subjects in Trials NP101-008 and NP101-009

	Number (%) of Subjects Reporting Event	
MedDRA Preferred Term	**≤ Age 43, N=345**	**≥ Age 43, N=317**
Application site reactions (bruising, discoloration, dryness, exfoliation, paresthesia, reaction, or vesicles)	94 (27.1)	81 (25.6)
Application site pain	66 (19.1)	51 (16.1)
Application site pruritus	46 (13.3)	55 (17.4)
Application site hypersensitivity	13 (3.8)	15 (4.7)
Respiratory tract infections	27 (7.8)	9 (2.9)

(Source: Sponsor's submission; Clinical Study Report, module 5.3.5.3, Tables 14.6.2 and 14.6.3)

Body Mass Index

The sponsor reported a median BMI of 25.7 mg/kg^2 based on all randomized population. There were slightly more reports of TEAE incidence of application site conditions in subjects with lower than the median BMI (Table 41 Treatment Emergent AEs Based on BMI in ≥2% of Subjects in Trials NP101-008 and NP101-009). Subjects with greater BMI than the median had more reports of gastrointestinal disturbances than subjects with lower BMI than the median. There were no differences reported by the sponsor for skin erythema scores post patch application or in the time to resolution of erythema in the two subgroups.

Table 41 Treatment Emergent AEs Based on BMI in ≥2% of Subjects in Trials NP101-008 and NP101-009

	Number (%) of Subjects Reporting Event	
MedDRA Preferred Term	**≤ BMI, N=335**	**≥ BMI, N=326**
Application site reactions (bruising, discoloration, dryness, exfoliation, paresthesia, reaction, vesicles, or warmth)	108 (32.4)	79 (24.2)
Application site pain	62 (18.5)	55 (16.9)
Application site pruritus	53 (15.8)	48 (14.7)
Application site hypersensitivity	17 (5.1)	11 (3.4)
Respiratory tract infections	29 (5.7)	17 (5.2)
Gastrointestinal disorders	3 (0.9)	7 (2.1)

(Source: Sponsor's submission; Clinical Study Report, module 5.3.5.3, Tables 14.6.8 and 14.6.9)

7.5.4 Drug-Disease Interactions

No formal drug-disease interaction studies have been conducted with NP101. Since this NDA is a 505(b)2 application, it relies on the same recommendations and cautions as described in the package insert of the reference listed drug, Imitrex®.

7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies have been performed with NP101. The sponsor, however, highlights the interaction of sumatriptan with MAO-A inhibitors with the following statement:

> Treatment with MAO-A inhibitors generally leads to an increase of sumatriptan plasma levels. In patients taking MAO-A inhibitors, sumatriptan plasma levels attained after treatment with recommended doses are 2-fold (following subcutaneous administration) and 7-fold (following oral administration) higher than those obtained without treatment with an MAO-A inhibitor.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity studies were conducted for this NDA.

7.6.2 Human Reproduction and Pregnancy Data

Eight pregnancies were reported in subjects during the Phase 3 clinical trials. Two subjects in the double-blinded, placebo-controlled efficacy study, NP101-007, received the placebo transdermal patch. Both subjects delivered full-term, healthy babies. A third subject in the long-term safety study, NP101-009, had enrolled in the trial but had not received treatment became pregnant and delivered a full-term, healthy baby.

The following is a summary of the pregnancy outcome of the 5 subjects who received NP101 patch treatment:

- Subject # 140-2060 (Study NP101-009) with history of a prior ectopic pregnancy, used 1 NP101 patch 25 days prior to positive home urine pregnancy test. Ultrasound 5 days later revealed an ectopic pregnancy. The subject's medical condition was complicated by ruptured ectopic pregnancy with significant hemoperitoneum (11 days after the positive pregnancy test) requiring surgery. The sponsor reported that SAE of severe severity was recorded with resolution in 2 days. The investigator deemed that the SAE was not related to the study drug.

- Subject #134-1178 (Study NP101-008) used a total 9 patches over 207 days (last patch used was 3 days before positive pregnancy test). A follow-up visit by the study site 3 months later reported that the patient was pregnant without complications and the estimated delivery date was (b) (6). The subject was subsequently lost to follow-up and no further information regarding pregnancy outcome could be obtained.

- Subject #112-2058 (Study NP101-009) used 1 patch and reportedly tested positive on urine pregnancy a week later on follow-up study visit. The subject elected to undergo a planned therapeutic abortion.

- Subject #108-2370 (Study NP101-009) used several patches over 3 months with last patch being applied 42 days before a positive home urine pregnancy test. Subject had a miscarriage in the first trimester (17 days after positive pregnancy test).

- Subject #112-2101 (Study NP101-009), used several patches over 11 months and had a positive pregnancy test at the final visit. Her last menstrual period was 73 days prior to positive pregnancy test. Delivery date is estimated to be (b) (6). The site reports that the subject is doing well and is without complications at the 3-month follow-up visit.

No conclusions can be drawn from the pregnancy outcomes outlined above due to the relatively low numbers of documented pregnancies. These low numbers are understandable as pregnancy was an exclusionary criterion in the clinical trials. Of

note, the sponsor provides an adequate summary of the current understanding of sumatriptan with regards to pregnancy outcomes and lactation. The sponsor presents post-marketing data for sumatriptan that includes results of the Sumatriptan and Naratriptan Pregnancy Registry. The sponsor also discusses results of several international post-marketing surveillance projects for pregnancy outcomes of women exposed to sumatriptan. The following is a summary of sumatriptan and pregnancy provided by the sponsor:

- Sumatriptan has not been shown to be mutagenic or clastogenic.
- The risk of all major birth defects following first-trimester exposure to sumatriptan is 4.6% (95% CI 2.9-7.2%). No consistent pattern of defects has been observed to date among the birth defects reported to the Sumatriptan and Naratriptan Registry.
- Additionally, observational/epidemiological studies have not observed a signal for major teratogenicity. Thus, there is no data that firmly establishes sumatriptan as a human teratogen, although there are no adequate and well-controlled studies in pregnant women. Sumatriptan is assigned FDA Pregnancy Category C status.
- Sumatriptan crosses the human placenta.
- Sumatriptan has been shown to be embryolethal in rabbits when given daily at a dose approximately equivalent to the maximum recommended single human subcutaneous dose of 6 mg on a mg/m2 basis.
- Sumatriptan is excreted in human breast milk.
- The effect of sumatriptan on spermatogenesis is not known.
- Sumatriptan should not cause contraceptive failure of commonly used oral contraceptives

7.6.3 Pediatrics and Assessment of Effects on Growth

The clinical development program for NP101 was performed in adults above the age of 18. The sponsor plans on conducting clinical trials with NP101 in the pediatric population.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose
Four cases of overdose from multiple NP101 patch applications were reported by the sponsor. One subject reported numerous adverse events which were all related to patch application site reaction. There were no reports of systemic adverse events from overdose. The 4 cases of overdose are summarized below.

Three subjects used a total of 3 patches each in a 24-hour period (Subject #'s: 105-1047, 108-2267, and 129-1163). No adverse events were reported with these applications.

One subject (#157-2097) used a total of 4 patches in a 34-hour time period. This subject applied 3 patches within a 24-hour period. The shortest length of time between patch applications was 6 hours apart. The 4 patches were applied to 4 different sites. There were 10 adverse events documented with the use of the 4 patches. Recovery time from the adverse events was 2 days. The subject continued in the trial using a total of 21 patches and having a total of 41 adverse events. There were no systemic adverse events reported.

Drug abuse, withdrawal and rebound
No studies have been conducted evaluating drug abuse, withdrawal, or rebound effects of NP101. There is no evidence of abuse potential based on the package insert for the reference listed product, sumatriptan succinate (Imitrex® injection).

7.7 Additional Submissions / Safety Issues

There were no data from submissions other than those noted above.

8 Postmarket Experience

NP101 is not approved for use and therefore there are no available post marketing data.

9 Appendices

9.1 Literature Review/References

Citations are noted in the text.

9.2 Labeling Recommendations

Recommendations regarding labeling have been deferred at this time.

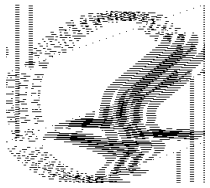
9.3 Advisory Committee Meeting

No advisory committee consideration was sought for this application.

9.4 Consultations

Division of Dermatology and Dental Products was consulted to evaluate hypersensitivity testing of NP101 sumatriptan iontophoretic transdermal system. Dr. Snezana Trajkovic conducted the review and her findings are presented in the Addendum below.

The following Addendum is the review by Snezana Trajkovic, MD, Medical Officer, Division of Dermatology and Dental Products (DDDP)



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring MD 20993

Tel 301-769-2110
FAX 301-796-9895

M E M O R A N D U M

Date: 6/3/11

From: Snezana Trajkovic, MD, Medical Officer, DDDP

Through: David Kettl, MD, Clinical Team Leader, DDDP
Susan Walker, MD, Division Director, DDDP

To: Eric Bastings, MD, Deputy Division Director, DNP
Nushin F. Todd, MD, Medical Officer, DNP

CC: Barbara Gould, CPMS, DDDP
Lana Y. Chen, Regulatory Project Manager, DNP
Mathew White, Regulatory Project Manager, DDDP

Re: DDDP Consult # 1319

Division of Neurology Products requested a consult: "Please evaluate hypersensitivity testing" related to Zelrix (Sumatriptan Iontophoretic Transdermal System, NDA (20-2278).

Materials Reviewed: Trial NP 101-008 and Trial NP 101-009

Conclusion:

Based on data from Trial NP 101-008 and Trial NP 101-009, Sumatriptan Iontophoretic Transdermal System has high irritation potential and is sensitizing. No cases of systemic hypersensitivity were reported during the conduct of Trials 101-008 and 101-009. Both trials had open label design, and therefore it is not possible to elucidate if the device or the drug component, or both, of this combination product, is responsible for the observed irritation and

sensitization. The potential for sensitization reactions are adequately addressed in proposed product labeling. The potential for irritation reactions should be further addressed in labeling.

Background:

Sumatriptan is a serotonin receptor agonist indicated for the acute treatment of migraine attacks. In the U.S. sumatriptan is currently available in three formulations – oral tablets, subcutaneous injection, and nasal spray. Sumatriptan was originally approved as Imitrex® injection on 12/28/1992.

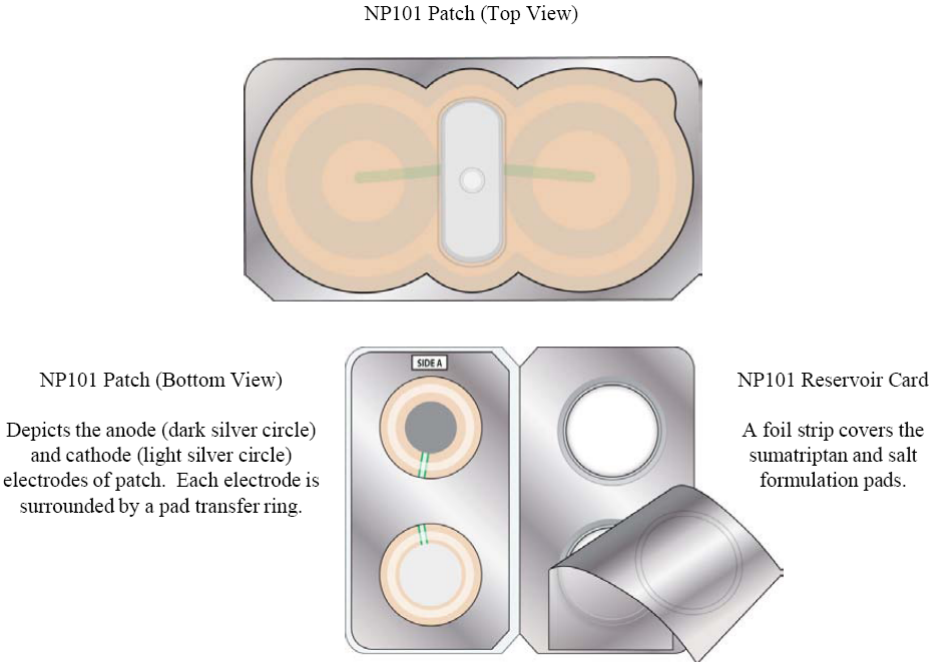
Zelrix™, Sumatriptan Iontophoretic Transdermal System is a thin, disposable, single-use patch with a self-contained electronic controller and a battery power source designed to deliver sumatriptan transdermally.

Sumatriptan Iontophoretic Transdermal System uses a very mild electrical field which is purported to propel molecules across the skin and into underlying tissue. Power is provided by incorporated lithium (b) (4) batteries designed to deliver a fixed, consistent charge to facilitate absorption through the skin.

Sumatriptan Iontophoretic Transdermal System employs the use of two electrodes with nonwoven pads placed on top of each electrode with one containing the drug formulation (anode), and the other containing a salt formulation (cathode). Application of a low electrical potential across the electrodes is proposed to result in the movement of ionized drug away from the electrode, through the skin, and into the tissue. The quantity of drug transported into the skin is proportional to the total current delivered and is dependent upon a number of criteria, including the molecular weight of the drug ion, drug concentration, and buffer concentration. During iontophoresis there is no mechanical penetration or disruption of the skin.

Figure 1 depicts Sumatriptan Iontophoretic Transdermal Patch.

Figure 1: NP101 Sumatriptan Iontophoretic Transdermal Patch



Source: Sponsor's submission

End of the Phase 2 meeting was held on 11/24/09. DDDP informed the sponsor of need to conduct dermal safety evaluation prior to approval. This was communicated to the sponsor in the letter on 3/5/10.

DNP requested consultation from DDDP as a follow up to this recommendation and after the sponsor provided information from ongoing long term Phase 3 trials (101-008 and 101-009), where NP101 was shown to be sensitizing. The sponsor requested a waiver for the need to conduct a dermal sensitization study. Considering that 21 day sensitization /irritation studies with the active drug containing patch cannot be safely performed (due to significant increase of drug exposure), DDDP provided the following recommendation to the sponsor on July 13, 2010:

> "You have submitted studies that are not adequate provocative dermal safety evaluations. However, since you have acknowledged that your product is sensitizing in actual use trials, the information collected during the open label phase 3 trials has the potential to be sufficient for product labeling".

Review

Trial NP 101-008

Trial Title

An Open-Label Study To Evaluate the Safety of NP101, a Sumatriptan Iontophoretic Transdermal Patch, in the Treatment of Acute Migraine over 12 Months.

Trial objective

The primary objective of this study was to evaluate the safety of long-term treatment with NP101.

Study population:

Subjects previously enrolled in Study NP101-007, who continued to be in good health and received treatment with the study patch under study NP101-007, were eligible for enrollment into this study.

Inclusion Criteria

Subjects were to meet all of the following inclusion criteria to enter the study:
1. Subject was previously enrolled in study NP101-007 and treated (patch activation) a qualifying migraine headache.
2. Subject was judged to be in good health, based upon the results of a medical history, physical examination, vital signs, and ECG. Subject did not have any clinically significant abnormal vital signs or ECG parameters. ECG was to be done at enrollment for NP101-008 unless the ECG for the Final Visit of study NP101-007 was conducted within 30 days.
3. Female subjects of childbearing potential (not surgically sterile or 2 years post menopausal) must have had a negative pregnancy test at enrollment.

Exclusion Criteria

Subjects were to be excluded from study participation for the following reasons:
1. Subject had less than two potential skin application sites.
2. Subject had clinically significant abnormal vital signs or ECG parameters or had an adverse event while participating in NP101-007 that precluded the continued treatment with the NP101 patch.
3. Subject had changes in their medical history or medication use that precluded their use of sumatriptan as per the approved Imitrex® product package insert or their safe use of NP101 as per the NP101 Investigator's Brochure.

4. Subject had or planned to start, stop, change treatment or dose of any of the following within 3 months prior to the subject's study Enrollment date and through the Final Visit: anxiolytics, lithium and other mood stabilizers such as valproate, carbamazepine or lamotrigine, hypnotics or antipsychotics.
5. Subject had taken non-triptan serotonergic drugs including selective serotonin reuptake inhibitor (SSRI), serotonin and norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressants (TCAs), monoamine oxidase inhibitor (MAOI) or preparations containing St. John's Wort within 1 month prior to enrollment and/or was planning to start any of these medications during the study (through Final Visit).
6. Female subjects who were pregnant, breast feeding, or of childbearing potential, and were not using or were unwilling to use an effective form of contraception during the study and for a period of 30 days following Final Visit. Acceptable methods of contraception included barrier method with spermicide, intrauterine device (IUD), steroidal contraceptive (oral, transdermal, implanted or injected) or abstinence. If the exclusive male partner was surgically sterile, this was acceptable.
7. Subject had participated in a clinical study within 30 days of enrollment (excluding NP101-007) or was planning to participate in another clinical study for the duration of NP101-008.

Trial design and procedures

This was an open-label, multicenter, phase 3 trial. One hundred eighty-three (183) subjects applied at least one NP101 patch in this study; a total of 2089 patches were applied and activated.

Subjects were treated for up to 12 months during which they were allowed to apply a maximum of six patches within a 30-day period. Subjects were not to apply more than two NP101 patches within a 24-hour period.

Patch application sites for subjects included right and left upper arms and right and left thighs. Patches were worn for four hours. A patch was not to be applied to a previous application site until the site remained erythema free for 72 hours.

The subject was to perform a self examination of the patch application site four hours after patch activation (within 10 minutes of patch removal) and again at 6, 12, and 24 hours.

Subject's skin irritation was rated using the following 5-point scale presented in Table 1:

Table 1: Subject Skin Self-examination Irritation Score

Score	Definition
0	No redness;
1	Minimal skin redness;
2	Moderate skin redness with sharp borders;
3	Intense skin redness with or without swelling;
4	Intense skin redness with blisters or broken skin

Source: Sponsor's submission

If the skin irritation score was not 0 at 24 hours, a self examination of the patch application site was to be completed daily until the score returned to 0. The subject recorded the skin irritation score in the Migraine Study Diary. A score of 3 or 4 was to be reported to the principal investigator or qualified designee and the subject was to be seen within 24 hours.

For subjects who had a skin irritation score of 3 or 4 at any visit, the principal investigator or qualified designee evaluated the subject and at the principal investigators discretion but, at minimum, a Unscheduled Follow-up Visit was to occur every 7 days (± 2 days) to complete another skin irritation examination with continued weekly follow-up until the skin irritation score was zero (0).

Any skin irritation score of 4, or if the event was deemed to be ACD (delayed hypersensitivity reaction) as assessed by the principal investigator or qualified designee, was to be reported as an expedited adverse event. Subjects who met all criteria under Definition for Putative Cases of Allergic Contact Dermatitis (ACD), as outlined below, were to be offered a referral for testing to determine whether they had developed topical sensitivity to sumatriptan.

If a subject reported a worsening of skin irritation after a period of improvement or whose skin irritation score significantly worsened on subsequent patch applications, the principal investigator or qualified designee was to assess whether the event was indicative of allergic contact dermatitis (ACD), a delayed hypersensitivity reaction.

"Definition for Putative Cases of Allergic Contact Dermatitis (ACD)

Subjects who meet all criteria under Clinical Course, Morphology and Symptoms should be referred for testing to determine whether they have developed topical sensitivity to sumatriptan.

Clinical Course:

- Sensitizing exposure required: Subject could have been previously exposed by taking subcutaneous sumatriptan or by transdermally administered sumatriptan through iontophoretic (NP101) use.

- Clinical lesions (see Morphology) appear after subsequent challenge(s) with antigen (i.e. sumatriptan). Lesions usually appear 24-72 hours after last exposure (but may develop as early as 5 hours or as late as 7 days after exposure).
- Clinical course characterized by crescendo phenomenon (clinical course / appearance worsens over time) followed by slower resolution.

Morphology:

- Most common: erythematous plaques (with or without edema) and / or erythemato-vesicular or erythemato-bullous eruptions, sometimes evolving to oozing dermatitis.
    a. Intense vesiculation increases suspicion of ACD. Pustules, necrosis, or ulceration rarely seen.
- Lesions are stronger in the contact area (but limits are usually ill-defined).
    b. Dissemination with distant lesions may occur.

Symptoms:

- Pruritus

All subjects who had a skin irritation score of ≥1 at the Final Visit were asked to continue to complete their Migraine Study Diary (recording daily assessments until the skin irritation score returns to zero) and to return for weekly Unscheduled Follow-up Visits until the principal investigator or qualified designee rated the skin irritation score a zero.

Investigator Skin Irritation Examinations

At Months 1, 2, 3, 6, 9, 12 (or Final Visit) and at all Unscheduled Follow-up Visits, the principal investigator or qualified designee examined all subject patch placement sites and scored the site with the worst skin irritation using the following scoring system presented in Table 2.

Table 2: Investigator's Skin Irritation Score

Score	Definition
0	No erythema
1	Minimal erythema
2	Moderate erythema with sharp defined borders
3	Intense erythema with or without edema
4[a]	Intense erythema with edema and blistering/erosion

[a]… A score of 4 required at all times the presence of intense erythema. If a blister or skin abrasion was noted on examination but there was no intense erythema, a lower score, commensurate with the level of the erythema, should have been assigned
Source: Sponsor's submission

Guidelines for applying and wearing the study patch were as follow:

• The patch was not to be applied over skin that was irritated. Skin was to be relatively hair free without scars or tattoos. The study patch was not to be applied over scratches or abrasions.
• The patch must lie flat over the skin for the patch to function properly. If the patch did not lie flat, it was to be removed.
• Subjects were to keep the patch dry and were not to bathe, shower or swim while wearing the study patch.
• The subject had four patch placement sites to choose from; right upper arm, right thigh, left upper arm, left thigh.
• If the subject chose to apply the patch to the right or left thigh, they were to be in a standing position when applying the patch.
• Subjects may have applied the NP101 study patch as a rescue medication if relief was not achieved two hours after initial patch activation (for pain scores of 1, 2 or 3). The patches were not to overlap each other and a patch was only applied to a previous application site if the self skin irritation score had remained 0 for at least 72 hours following patch removal.
• If the formulation from the under the patch leaked onto the subject's arm and/or thigh/leg, the subject was to clean the affected area with soap and water.
• It was to be clearly understood by the subject during their instruction on patch application that both medication pads must lie flat over the electrodes before applying and activating the NP101 patch, and that the consequence of not having the pads directly over the electrodes during patch application and activation may be an intense skin reaction with pronounced redness, blisters and or broken skin.
• The subject was not to use any ergot or other triptan medications 24 hours before or after any NP101 patch activation.
• The subject was not to use any analgesic or antiemetic medication 8 hours prior to initial NP101 patch activation.
• The subject was not to use any medications to treat their initial acute migraine symptoms (i.e. pain, nausea, photophobia or phonophobia) within the first two hours after the initial NP101 patch activation.
• When treating an initial acute qualifying migraine, the subject was to rate the severity of their migraine using the Diary Headache Pain Severity scores. Subjects should not have used the NP101 study patch within 24 hours prior to treatment of the initial acute migraine attack.
• No more than two NP101 patches were to be applied in a 24-hour period.
• The NP101 transdermal iontophoretic patch was not to be applied or used during an MRI scan, and if already being used, the NP101 transdermal iontophoretic patch was to be removed.

There were seven scheduled study visits: Study Visit 1 (Enrollment), Visit 2 (Month 1), Visit 3 (Month 2), Visit 4 (Month 3), Visit 5 (Month 6), Visit 6 (Month 9) and Visit 7 (Month 12 or Final Visit). In addition, subjects returned to the investigative site as needed to turn in and obtain additional study patches (Patch Dispensing Visits), or when required for additional skin irritation assessments or follow-up (Unscheduled Visits).

Results of **Trial NP 101-008**

A total of 2089 patches were used by 183 subjects over the 12-month period of study. More than half of all treated subjects (55.7%) used at least 6 patches during the study, and 30.6% used at least 12 patches. A total of 76 subjects met the definition of a 6-month completer (subjects who were enrolled for at least 166 days and applied at least 6 patches within the first 180 days of enrollment) and 51 subjects met the definition of a 12-month completer (6-month completers who were enrolled for at least 346 days and applied at least 9 patches within the first 360 days of enrollment).

Skin irritation evaluation

Subject's skin irritation evaluation results

Subjects performed their own examination of the patch site at 4, 6, 12, and 24 hours post patch activation, and daily thereafter until resolution. If subject's irritation score was reported to be 3 or 4, principal investigator or qualified designee would evaluate the patient within 24 hour of report.

At the time of patch removal (4 hours post patch activation), subject self-examination skin irritation scores indicated no redness or minimal redness for 38.2% of all patches scored at that time point during the study, moderate redness for 54.0%, and intense redness for 7.8%.

By 24 hours after patch application, 65.4% of all patch applications had minimal or no redness, while 31.2% were scored as having moderate redness, 45 patch application sites (2.3%) had a score of 3 (intense redness with or without swelling), and 20 (1.0%) had a score of 4 (intense redness with blisters or broken skin).

By 6 days post-application, six application sites still had a score of 3 and seven had a score of 4.
By 11 days post-application, there were two patch sites with a score of 3 (none with a score of 4).
By 16 days post-application, there were no scores of 3 or 4. The mean time to resolution of erythema (based on a total of 1871 patches for which complete data were available) was 3.5 days and the median time to resolution of erythema was 2.0 days.

Results from subject's skin irritation evaluation revealed that NP101 transdermal iontophoretic patch was irritating (24 hours post patch application, over 30% of subjects had moderate to intense redness at the application site).

Subject's self-examination skin irritation scores for the first 24 hours are reported in Table 3.

Table 3: Subject's Self-examination Skin Irritation Scores

	Time Point Post Patch Application (N=183)			
Skin Assessment Scores	**4 Hours**	**6 Hours**	**12 Hours**	**24 Hours**
Number of patches scored	1920	2019	1950	1917
Distribution, n (%)[a]				
No redness	200 (10.4)	366 (18.1)	515 (26.4)	792 (41.3)
Minimal redness	534 (27.8)	562 (27.8)	565 (29.0)	462 (24.1)
Moderate redness	1037 (54.0)	959 (47.5)	788 (40.4)	598 (31.2)
Intense redness with or without swelling	139 (7.2)	125 (6.2)	71 (3.6)	45 (2.3)
Intense redness with blisters or broken skin	10 (0.5)	7 (0.3)	11 (0.6)	20 (1.0)
Missing[b]	7	2	3	5
Mean (SD)	1.6 (0.79)	1.4 (0.87)	1.2 (0.90)	1.0 (0.96)
Median	2.0	2.0	1.0	1.0
Minimum, Maximum	0, 4	0, 4	0, 4	0, 4

[a] The denominator is the total number of patches with a score at the respective time point.
[b] Missing is not included in the denominator.
Source: Sponsor's submission

When subject's skin irritation scores at 24-hours, by month, were evaluated the following results were obtained:

From Month 1 to Month 2, there appeared to be some increase in the percentage of subjects with 24-hour skin irritation scores of 3 or 4 along with an increase in mean score from 1.0 to 1.3; however, the difference in the number of patch applications assessed (515 and 157, respectively) makes it difficult to draw conclusions from these data.

For Month 3 through Month 11, when the number of patches scored per month was fairly stable, there was no evidence of an increase in skin irritation over time, with mean scores ranging from 0.7 to 1.2.

Summary of subject skin irritation assessment at 24 hours after patch activation by study month are presented in Table 4.

Table 4: Summary of Subject Skin Irritation Assessment at 24 Hours after Patch Activation by Study Month (Safety Population)

	Subject Skin Irritation Scores at 24 Hours after Patch Activation (N=183)											
	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Number scored	515	157	117	112	143	140	132	108	141	129	135	87
Distribution, %[a]												
Score = 0	34.6	32.5	40.2	40.2	37.8	37.9	50.8	50.0	45.4	52.7	48.1	51.7
Score =1	30.5	22.9	25.6	17.0	22.4	22.1	12.1	23.1	23.4	24.8	24.4	20.7
Score = 2	32.2	33.8	29.1	33.0	36.4	37.1	34.1	26.9	30.5	21.7	25.9	27.6
Score = 3	1.6	7.6	3.4	4.5	3.5	2.9	3.0	0	0.7	0.8	0.7	0
Score = 4	1.2	3.2	1.7	5.4	0	0	0	0	0	0	0.7	0
Mean	1.0	1.3	1.0	1.2	1.1	1.1	0.9	0.8	0.9	0.7	0.8	0.8
SD	0.91	1.09	1.00	1.17	0.94	0.93	0.98	0.85	0.88	0.83	0.90	0.86
Median	1.0	1.0	1.0	1.0	1.0	1.0	0.0	0.5	1.0	0.0	1.0	0.0
Min, Max	0, 4	0, 4	0, 4	0, 4	0, 3	0, 3	0, 3	0, 2	0, 3	0, 3	0, 4	0, 2

[a] Percentage based on the total number of patches with a 24-hour post patch activation score at the respective study month.
0 = no redness; 1 = minimal redness; 2 = moderate redness; 3 = intense redness with or without swelling; 4 = intense redness with blisters or broken skin; SD = standard deviation.
Source: Sponsor's submission

Investigator's Skin Irritation Assessment

At each visit, the Investigator or other qualified personnel examined all patch placement sites and scored the site with the worst skin irritation score using the scale shown in Table 5.

The majority of subjects (>74%) had no erythema at patch application sites. Except for one subject at Month 6, and four subjects at Month 12/Final Visit, the remaining subjects evaluated at each visit had minimal or moderate erythema at the site of worst irritation.
There were two subjects with skin irritation scores rated as 4 by the Investigator at the Month 12/End of Study visit and three other subjects with scores of 4 at Unscheduled Visits. All of these subjects were discontinued from study due to AE (application site hypersensitivity /allergic contact dermatitis).

Table 5: Investigator Highest Skin Assessment by Study Month

Visit	Assessment[a]	NP101 N=183 (%)
Month 1	No erythema	109 (74.7)
	Minimal erythema	28 (19.2)
	Moderate erythema	9 (6.2)
	Intense erythema /with or without edema	0
	Intense erythema /with edema and blistering	0
	Missing	37
Month 2	No erythema	108 (81.8)
	Minimal erythema	19 (14.4)
	Moderate erythema	5 (3.8)
	Intense erythema/with or without edema	0
	Intense erythema /with edema and blistering	0
	Missing	51
Month 3	No erythema	80 (85.1)
	Minimal erythema	12 (12.8)
	Moderate erythema	2 (2.1)
	Intense erythema/with or without edema	0
	Intense erythema /with edema and blistering	0
	Missing	89
Month 6	No erythema	57 (82.6)
	Minimal erythema	8 (11.6)
	Moderate erythema	3 (4.3)
	Intense erythema/with or without edema	1 (1.4)
	Intense erythema /with edema and blistering	0
	Missing	114

Table 5: Investigator Highest Skin Assessment by Study Month (continued)

Visit	Assessment	NP101 N=183 (%)
Month 9	No erythema	59 (92.2)
	Minimal erythema	5 (7.8)
	Moderate erythema	0
	Intense erythema/with or without edema	0
	Intense erythema /with edema and blistering	0
	Missing	119
Month 12/ End of Study	No erythema	136 (84.5)
	Minimal erythema	13 (8.1)
	Moderate erythema	8 (5.0)
	Intense erythema/with or without edema	2 (1.2)
	Intense erythema /with edema and blistering	2 (1.2)
	Missing	22

[a] Missing is not included in the denominator.

Source: Sponsor's submission

Investigator's assessment of irritation revealed that NP101 transdermal iontophoretic patch was not as irritating (more then 90% of subjects had no or minimal erythema) in comparison to subject's assessment (24 hours post patch application, over 30% of subjects had moderate to intense redness) at the application sites.
The disparity of subject's and investigator's skin irritation assessments were due to difference of timing of assessments (subject's assessment was performed 4, 6, 12, and 24 hours post patch activation while investigator's assessment was performed during regular office visits irrespective of time of patch application).

Allergenicity Evaluation

A total of 14 cases of allergic contact dermatitis (ACD) were identified by medical specialist review including those with a recorded AE of application site hypersensitivity /ACD. Of these, six cases fully met the putative ACD diagnosis criteria utilized by the medical and dermatology review group and were deemed to be "probable"; the remaining 8 cases were deemed "possible".

The overall rate of ACD with NP101 in subjects with at least two patch applications was 3.7% (6/164) when "probable" cases were considered, and 8.5% (14/164) when "possible" and "probable" cases were included.

Rates of ACD appeared to be decreasing after use of nine or more patches. No ACD cases were observed after the use of 12 or more patches. In the opinion of this reviewer the reason for decrease in number of ACD with continuous patch use is due to discontinuation of subjects who developed ACD with patch use at earlier time points during the trial.

Adverse events

The most frequently reported AEs, experienced by 45% of all treated subjects, were in System Organ Class (SOC) of "Application site conditions", and at the Proffered Term (PT) application site pruritus (21.9%), application site pain (21.3%), application site hypersensitivity (ACD; 6.0%), application site exfoliation (4.9%), application site reaction (4.9%), application site paraesthesia (4.4%), and application site vesicles (3.8%).

Discontinuations due to adverse events

Twenty-five (25) subjects (13.7%) discontinued study due to adverse events. One subject (0.5%) discontinued due to nausea; one subject discontinued due to dizziness; and 23 subjects (12.6%) discontinued due to application site conditions.

The "APPLICATION SITE CONDITIONS" [25 (13.7%)] leading to discontinuation were:

- Application site hypersensitivity (8, 4.4%);
- Application site pain (6, 3.3%);
- Application site discoloration (2, 1.1%);
- Application site pruritus (3, 1.6%);
- Application site anesthesia, bruising, discomfort, reaction, and vesicles (1 subject each, 0.5%).

Two serious adverse events were reported during the study: severe vertigo considered unrelated to study drug, and severe dehydration considered unrelated to study drug.

Trial NP 101-009

Trial Title

An Open-Label Study To Evaluate the Safety of NP101, a Sumatriptan Iontophoretic Transdermal Patch, in the Treatment of Acute Migraine over 12 Months

Trial objective

The primary objective of this study was to evaluate the safety of long-term treatment with NP101.

Trial design and procedure

This was an open-label design to assess the long term safety of NP101 (sumatriptan iontophoretic transdermal patch).

Study population

Please see Inclusion Criteria and Exclusion Criteria for Trial NP 101-008

Trial design and procedures

Please see trial design and procedures for Trial NP 101-008

Results of Trial NP 101-009

Subject's Self-examination Skin Irritation Scores

Subjects performed their own examination of the patch site at 4, 6, 12, and 24 hours post patch activation, and daily thereafter until resolution, and scored skin irritation using the scale shown in Table 6.

Four hundred seventy nine (479) subjects applied at least one NP101 patch in this study; a total of 5562 patches were applied and activated. 63.5% of subjects used at least 6 patches during the study, and 41.3% used at least 12 patches.

At the time of patch removal (4 hours post patch activation), subject self-examination skin irritation scores indicated no redness or minimal redness for 49.3% of all patches scored at that time point during the study, moderate redness for 45.3%, and intense redness with or without swelling for 5.1% and intense redness with blisters or broken skin in 0.4%.

By 24 hours after patch application, 77.7% of all patch applications had minimal or no redness, while 19.8% were scored as having moderate redness, 2.1% had a score of 3 (intense redness with or without swelling), and 0.4% had a score of 4 (intense redness with blisters or broken skin).

By 16 days post-application, there were 2 scores of 3 and one score of 4. The mean time to complete resolution of erythema (based on a total of 5562 patches for which complete data were available) was 2.7 days and the median time to resolution of erythema was 1.0 day.

The results from subject's skin irritation evaluation revealed that NP101 transdermal iontophoretic patch was irritating (24 hours post patch application, over 20% of subjects had moderate to intense redness of application sites).

A summary of subject skin irritation assessments at patch removal (4 hours), 6 hours, 12 hours and 24 hours post patch activation is shown in Table 8.

Table 8: Summary of Subject Skin Assessment at Each Time Point within 24 hours after Patch Application (Safety Population)

	Time Point Post Patch Application (N=479)			
Skin Assessment Scores	**4 Hours**	**6 Hours**	**12 Hours**	**24 Hours**
Number of patches scored	5458	5438	5390	5342
Distribution, n (%)[a]				
No redness	1084 (19.9)	1496 (27.5)	2086 (38.7)	3091 (57.9)
Minimal redness	1605 (29.4)	1607 (29.6)	1645 (30.5)	1059 (19.8)
Moderate redness	2473 (45.3)	2108 (38.8)	1481 (27.5)	1060 (19.8)
Intense redness with or without swelling	276 (5.1)	208 (3.8)	161 (3.0)	113 (2.1)
Intense redness with blisters or broken skin	20 (0.4)	19 (0.3)	17 (10.3)	19 (0.4)
Missing[b]	3	7	7	7
Mean (SD)	1.4 (0.87)	1.2 (0.90)	1.0 (0.90)	0.7 (0.89)
Median	2.0	1.0	1.0	0.0
Minimum, Maximum	0, 4	0, 4	0, 4	0, 4

[a] The denominator is the total number of patches with a score at the respective time point.
[b] Missing is not included in the denominator.
Source: Sponsor's submission

When subject skin irritation assessment scores by study month were analyzed by subset according to cumulative patch usage (above or below the median), there were no overall trends to suggest that subjects whose cumulative patch usage was above the median experienced any greater skin irritation than did subjects whose cumulative patch usage was equal to or below the median.

From Month 1 through Month 7, when more than 100 patches per month were used, the percentage of patches with 24-hour skin irritation scores of 3 or 4 was similar over time with mean scores ranging from 0.5 to 0.7. Subject skin irritation scores on subsequent days post patch application also did not show any trends towards an increase in skin irritation with successive patch usage.

The mean time to complete resolution of erythema at patch application sites was 2.7 days and the median time to resolution of erythema was 1.0 day.

Summary of skin irritation assessment at 24 hours after patch activation by study month are presented in Table 9.

Table 9: Summary of Subject Skin Irritation Assessment at 24 Hours after Patch Activation by Study Month (Safety Population)

	Subject Skin Irritation Scores at 24 Hours after Patch Activation (N=479)											
	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Number scored	1719	826	697	568	547	366	238	222	104	24	25	5
Distribution, %[a]												
Score = 0	53.3	58.8	59.4	62.3	63.8	57.4	61.8	54.1	71.2	33.3	36.0	40.0
Score =1	25.3	19.0	17.2	15.5	15.9	19.1	15.5	23.4	8.7	8.3	4.0	20.0
Score = 2	18.6	19.4	20.4	20.1	17.6	22.1	21.8	20.3	18.3	58.3	60.0	40.0
Score = 3	2.5	2.2	2.6	1.6	2.6	0.8	0.4	2.3	1.9	0	0	0
Score = 4	0.2	0.6	0.4	0.5	0.2	0.5	0.4	0	0	0	0	0
Mean	0.7	0.7	0.7	0.6	0.6	0.7	0.6	0.7	0.5	1.3	1.2	1.0
SD	0.87	0.90	0.91	0.89	0.88	0.88	0.87	0.87	0.86	0.94	0.97	1.00
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.0	2.0	1.0
Min, Max	0, 4	0, 4	0, 4	0, 4	0, 4	0, 4	0, 4	0, 3	0, 3	0, 2	0, 2	0, 2

[a] Percentage based on the total number of patches with a 24-hour post patch activation score at the respective study month.
0 = no redness; 1 = minimal redness; 2 = moderate redness; 3 = intense redness with or without swelling; 4 = intense redness with blisters or broken skin; SD = standard deviation.
Source: Sponsor's submission

Investigator's Skin Irritation Assessment

At each visit, the Investigator or other qualified personnel examined all patch placement sites and scored the site with the worst skin irritation score using the scale shown in Table1.
There were 15 subjects with skin irritation scores rated as 4 by the Investigator during at least one Study visit. Fourteen of these subjects with AEs led to discontinuation of study drug. Two subjects did not discontinue study due to an AE but were lost to follow-up.

Investigator's assessment of irritation revealed that NP101 transdermal iontophoretic patch was not as irritating (more then 90% of subjects had no or minimal erythema) in comparison to subject's assessment (24 hours post patch application, over 20% of subjects had moderate to intense redness) at the application sites.
The disparity of subject's and investigator's skin irritation assessments were due to difference of timing of assessments (subject's assessment was performed 4, 6, 12, and 24 hours post patch activation while investigator's assessment was performed during regular office visits irrespective of time of patch application).

Allergenicity Evaluation

A total of 30 potential cases of allergic contact dermatitis (ACD) were identified by medical and dermatology ACD expert review. Of these, 12 cases fully met the putative ACD diagnosis criteria utilized by the review group and were deemed to be "probable"; the remaining 18 cases were deemed "possible". The overall rate of putative ACD with NP101 use in subjects with at least two patch applications was 2.7% (12/442) when "probable" cases were considered and 6.8% (30/442) when "possible" and "probable" cases were included.

Discontinuations

Sixty-two (12.9%) subjects were discontinued due to AEs, primarily patch application site disorders. One subject (0.2%) each discontinued due to supraventricular tachycardia, diarrhea, nausea, herpes zoster, headache, and rash macula-papular. Three subjects (0.6%) discontinued due to depression and 53 subjects (11.1%) discontinued due to application site conditions.

The "APPLICATION SITE CONDITIONS" [62 (12.9%)] leading to discontinuation were:

- Application site hypersensitivity (15, 3.1%)
- Application site pain (15, 3.1%)
- Application site discoloration (5, 1.0%)
- Application site irritation (5, 1.0%)
- Application site pruritus (5, 1.0%)
- Application site reaction (2, 0.4%)
- Application site bruising, burn, induration, paraesthesia, and rash (1 subject each, 0.2%).

Application site hypersensitivity was evaluated as described in **"Definition for Putative Cases of Allergic Contact Dermatitis (ACD).**

Adverse Events

The most frequently reported AEs, were in SOC "Application site conditions", and at PT level were: application site pain (16.3%), application site pruritus (12.7%), application site reaction (6.1%), application site paraesthesia (5.4%), application site dryness (5.0%), application site discoloration (4.0%) and application site hypersensitivity (3.5%).

Seven serious adverse events were reported during the study: nephrolithiasis, headache, back pain, ectopic pregnancy, supraventricular tachycardia, syncope, and atrial fibrillation. None of the events were considered by the investigator to be related to study medication.

Conclusion

Based on data from Trial NP 101-008 and Trial NP 101-009, Zelrix™, Sumatriptan Iontophoretic Transdermal System has significant irritation potential and is sensitizing. No cases of systemic hypersensitivity were reported during the conduct of Trials 101-008 and 101-009. There is no record that any subject required epinephrine or other emergency care for treatment of anaphylaxis. Since both trials were open label, and no placebo containing patches were evaluated, it is not possible to conclude if device or drug component of this combination product is responsible for irritation and sensitization. Information on sensitization potential was addressed in product labeling. Information on irritation potential of patch product should be addressed adequately in labeling.

The sponsor proposed under section (b) (4)

(b) (4)

The proposed labeling adequately informs health care professional of potential for allergic contact dermatitis and systemic sensitization after exposure to Zelrix, and the possible implications for other dosage forms of sumatriptan.

Inclusion of labeling from other approved products in the sumatriptan class is recommended given the adverse reaction experience related to hypersensitivity from currently marketed sumatriptan products.

Irritation potential of the patch product was addressed in labeling in section (b) (4)

However, Zelrix may cause irritation even with proper use (not only with improper application) and labeling should adequately inform prescribers of this potential adverse reaction.

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

/s/

NUSHIN F TODD
08/25/2011

ERIC P BASTINGS
08/26/2011