CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207962Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 207962	Submission Date: August 28, 2017
Proposed Brand Name	ZTlido
Generic Name	Lidocaine patch 1.8%
Reviewer	Wei Qiu, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	DCPII
OND division	DAAAP
Sponsor	Scilex Pharmaceuticals, Inc.
Relevant IND(s)	IND 111537
Submission Type	Resubmission; 505(b)(2)
Formulation; Strength(s)	Topical patch; 1.8%
Dosage and Administration	Up to 3 patches for up to 12 hours in a 24-hour period (12 hours on and 12 hours off)
Indication	Relief of pain associated with post-herpetic neuralgia

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the resubmission of NDA 207962 dated August 28, 2017 and finds it acceptable. Labeling negotiation with the sponsor is still ongoing.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Pivotal comparative BA study SCI-LIDO-PK-002A demonstrated equivalent Cmax and AUC between lidocaine patch 1.8% and Lidoderm patch 5%,
General dosing instructions	Up to 3 patches for up to 12 hours in a 24-hour period (12 hours on and 12 hours off)
Dosing in patient subgroups (intrinsic and extrinsic factors)	Same as the list drug product Lidoderm patch 5%.
Labeling	Ongoing negotiation
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in pivotal comparative BA and other clinical pharmacology studies.

1.2 Summary of Clinical Pharmacology Findings

In the complete response letter dated May 10, 2016, Deficiency #4 is stated as "The comparative bioavailability study, SCI-LIDO-PK-001, intended to bridge to the Agency's previous findings of efficacy and safety for Lidoderm patch 5%, cannot be used to establish bioequivalence because surgical tape was used to secure the Lidoderm 5% patches, and adequate evidence was not provided to justify that the use of tape would not affect lidocaine absorption from Lidoderm patch 5%. To address this deficiency, conduct a new adequately-designed comparative bioavailability study to demonstrate equivalent systemic exposure to Lidoderm patch 5%. The list drug product, Lidoderm patch 5%, must be used according to the approved package insert (e.g., without use of an overlay or tape). Additional data from Study SCI-LIDO-HEX-001 submitted during the review cycle were not reviewed. You may reference the submission as part of your response to the deficiencies cited in this letter".

In this resubmission, the Sponsor submitted a comparative bioavailability study (SCI-LIDO-PK-002A) to address the deficiency #4 on appropriate PK bridging to the list drug product, Lidoderm patch 5%. Study SCI-LIDO-PK-002A demonstrated that three patches of lidocaine patch 1.8% provided comparable lidocaine systemic exposure as three patches of Lidoderm patch 5% with no tape reinforcement. Therefore, the PK bridging to the Agency's previous findings on efficacy and safety for Lidoderm patch 5% is adequately established. The Office of Study Integrity and Surveillance (OSIS) recommended to accept data from pivotal BA study SCI-LIDO-PK-002A without an on-site inspection (Dr. Shila S Nkah's memo dated 10/13/17). In addition, the sponsor evaluated the effect of heat and exercise on lidocaine absorption from lidocaine patch 1.8% while the subjects were wearing the patches in Study SCI-LIDO-HEX-001.

Comparative Bioavailability between Lidocaine Patch 1.8% and Lidoderm Patch 5% without Tape Reinforcement

Three patches of lidocaine patch 1.8% (test) exhibited equivalent lidocaine Cmax and AUC values and similar Tmax values to those for three patches of Lidoderm patch 5% (reference) without tape reinforcement (see **Tables 1** and **2**). Median (min, max) Tmax values were 13.9 (4.0, 18.0) h and 11.0 (4.0, 17.9) h for lidocaine patch 1.8% and Lidoderm patch 5%, respectively. The Cmax, AUCt and AUCinf for lidocaine patch 1.8% and Lidoderm patch 5% met the bioequivalent (BE) criteria. The point estimate of the geometric mean ratio (lidocaine patch 1.8%/Lidoderm patch 5%) for lidocaine Cmax, AUCt and AUCinf were 90.7%, 89.1%, and 88.6%, respectively. The corresponding 90% confidence intervals (CIs) were 85.0 – 96.8%, 84.9 – 93.5%, and 92.8 – 98.9%, respectively. All these 90% CIs fell within the 80 to 125% BE limit.

Table 1 Mean (SD) Lidocaine PK Parameters for Three Patches of Lidocaine Patch 1.8% and Three Patches of Lidoderm Patch 5% (Study SCI-LIDO-PK-002A)

Pharmacokinetic Parameters	Lidocaine Patch 1.8% Mean ± SD (N=54)	Lidoderm® Patch 5% Mean ± SD (N=54)
C_{max} (ng/mL)	75.1 ± 28.0	86.6 ± 42.3
T_{max} (hr)	13.9 (4.0, 18.0)	11.0 (4.0, 17.9)
AUC_{0-t} (ng·hr/mL)	1242.9 ± 432.5	1420.8 ± 586.0
$AUC_{0-\infty}$ (ng·hr/mL)	1253.7 ± 432.5	1435.5 ± 588.9*
$T_{½}$ (hr)	5.4 ± 1.0	6.2 ± 1.6*

* N = 53

T_{max} is reported as median value (range)

Table 2 Summary of Equivalence Analyses for the Lidocaine PK of Three Patches of Lidocaine Patch 1.8% and Three Patches of Lidoderm Patch 5% (Study SCI-LIDO-PK-002A)

Pharmacokinetic Parameter	Geometric Mean		Ratio of Geometric Means	90% CI	
	Lidocaine Patch 1.8%	Lidoderm® Patch 5%		Lower	Upper
C_{max} (ng/mL)	70.6	78.1	90.7	85.0	96.8
AUC_{0-t} (ng·hr/mL)	1173.0	1320.6	89.1	84.9	93.5
AUC_{0-inf} (ng·hr/mL)	1184.4	1335.8	88.6	84.4	93.0

Appears this way on original

Effect of Heat and Exercise on Lidocaine PK of Licocaine Patch 1.8%

Use of heating pad on top of the lidocaine patches 1.8% immediately after patch application and at 8.50 hours post-application (heating pad was left in place for 20 min) increased lidocaine Cmax by 46% but did not affect the AUCt or AUCinf as compared to normal conditions. The point estimate of the geometric mean ratio (heating pad/normal condition) for lidocaine Cmax, AUCt and AUCinf were 146.57%, 108.02%, and 107.87%, respectively. The corresponding 90% confidence intervals (CIs) were 123.71 – 173.66%, 95.34 – 122.40%, and 95.46 – 121.79%, respectively. The 90% CIs for AUCt and AUCinf ratios fell within the 80 to 125% BE limit. Moderate exercise (biking immediately after patch application and at 2.50, 5.50, and 8.50 hours post-patch application for 30 minutes) did not affect lidocaine PK (**Table 3** and **4**). The point estimate of the geometric mean ratio (exercise/normal condition) for lidocaine Cmax, AUCt and AUCinf were 95.14%, 90.25%, and 90.53%, respectively. The corresponding 90% confidence intervals (CIs) were 80.30 – 112.73%, 79.65 – 102.26%, and 80.15 – 102.25%, respectively. No tape reinforcement was used during the study.

Table 3 Summary of Lidocaine PK Parameters for the Effect of Heat (Treatment B) and Exercise (Treatment A) on Lidocaine PK of Three Patches of Lidocaine Patch 1.8% in Comparison to Normal Condition (Treatment C) (Study SCI-LIDO-HEX-001)

Parameter (Unit)	Mean ± SD (Un-transformed data)		
	Treatment (A)	Treatment (B)	Treatment (C)
C_{max} (ng/mL)	90.47750 ± 25.413083	160.27500 ± 100.061002	97.59333 ± 36.869199
$AUC_{0\rightarrow t}$ (hr. ng/mL)	1328.80587 ± 461.660141	1718.70939 ± 1004.00502	1487.39290 ± 590.006714
$AUC_{0\rightarrow\infty}$ (hr. ng/mL)	1344.07581 ± 458.186710	1731.27168 ± 1005.03640	1501.09829 ± 588.427583
$AUC_{\%Extrapolation}$	1.36226 ± 2.211383	0.89693 ± 1.112316	1.07191 ± 1.534819
T_{max} (hr)*	9.00 (9.00-18.00)	9.00 (9.00-16.05)	11.50 (9.00-14.00)
K_{el} (hr^{-1})	0.12803 ± 0.024237	0.13509 ± 0.029065	0.13874 ± 0.029814
$t_{½}$ (hr)	5.602 ± 1.1134	5.390 ± 1.3381	5.230 ± 1.2029

Table 4 Summary of Equivalence Analyses for the Effect of Heat (Treatment B) and Exercise (Treatment A) on Lidocaine PK of Three Patches of Lidocaine Patch 1.8% in Comparison to Normal Condition (Treatment C) (Study SCI-LIDO-HEX-001)

PK Parameter	Ratio % (A/C)	90% CI (A/C)	Ratio % (B/C)	90% CI (B/C)
Cmax	95.14	80.30 – 112.73	146.57	123.71 – 173.66
AUC0-t	90.25	79.65 – 102.26	108.02	95.34 – 122.40
AUC0-inf	90.53	80.15 – 102.25	107.83	95.46 – 121.79

In Study SCI-LIDO-PK-001 submitted in the original submission, moderate heat (15 min heating pad immediately prior to patch application) and moderate exercise (walking at a moderate pace on a treadmill for approximately 20 minutes beginning approximately 30 minutes prior to the application) engaged prior to patch administration did not affect systemic lidocaine concentrations as compared to a normal patch application (**Table 5**). The patches were reinforced with tape.

Table 5 Effects of Moderate Heat and Exercise Prior to Patch Application on Lidocaine PK for Lidocaine Patch 1.8% as Compared to Normal Patch Application (Study SCI-LIDO-PK-001)

Treatment Arm (Condition)	N (Male/Female)	C_{max} (ng/mL) [±SD]	T_{max}[1] (hour) [range]	AUC_{0-t} (ng·h/mL) [±SD]	AUC_{0-inf} ng·h/mL [±SD]	$T_{½}$ hr [±SD]	K_e hr^{-1} [±SD]
Lidocaine patch 1.8% (heat)	14 (5 M / 9 F)	95.26 (34.69)	13.93 (12.9, 16.0)	1429.58 (458.62)	1453.65 (463.02)	5.71 (0.99)	0.12 (0.02)
Lidocaine patch 1.8% (exercise)	14 (5 M/9 F)	103.69 (31.77)	13.46 (11.2, 16.0)	1576.67 (531.49)	1624.13 (534.81)	5.64 (0.84)	0.13 (0.02)
Lidocaine patch 1.8% (normal)	14 (5 M/9 F)	102.81 (28.23)	12.99 (13.0, 14.0)	1505.77 (559.87)	1550.76 (525.89)	5.34 (1.03)	0.13 (0.03)

[1] Median value [range]

2 QBR

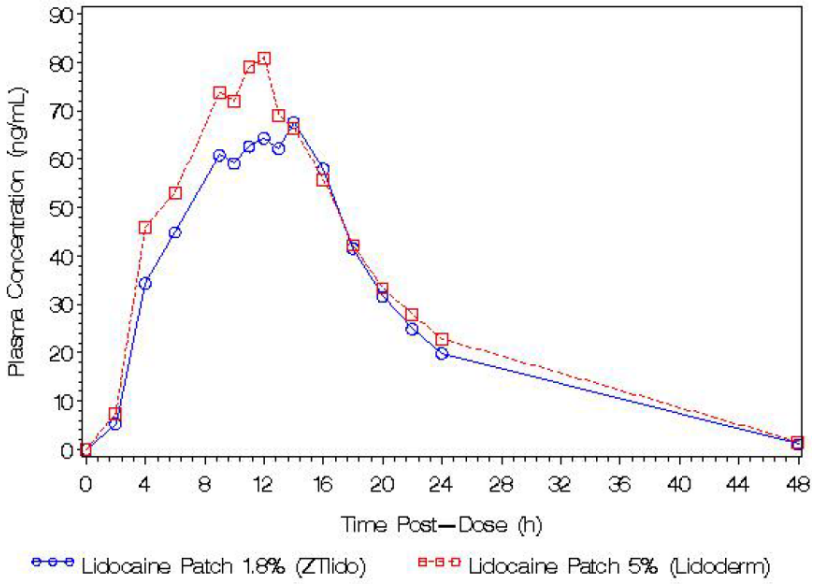
2.1 *What is the comparative bioavailability of lidocaine following the application of lidocaine patch 1.8% in comparison to Lidoderm patch 5% without tape reinforcement?*

Three patches of lidocaine patch 1.8% exhibited similar lidocaine systemic exposures in comparison to three patches of Lidoderm patch 5% without tape reinforcement on patches during the administration period.

In Study SCI-LIDO-PK-002A, the relative bioavailability of lidocaine was performed as a single dose, two-way cross-over design with the application of three patches of either the lidocaine patch 1.8% or the listed drug product, Lidoderm patch 5%. There is a washout period of 7 days between treatments. Each patch was applied to a defined area of normal skin on the back of each volunteer for 12 hours. Blood samples for PK determination were collected from each subject at pre-dose, and then at 2, 4, 6, 9, 10, 11, 12, 13, 14, 16, 18, 20, 22, 24, and 48 hours post-dose patch application. At the time of each PK blood draw, any part of the patch that was observed to be lifting may have been pressed down firmly (for not more than 10 seconds).

The mean lidocaine plasma concentration-time profiles are shown in **Figure 1**. The PK results and statistical analysis results for equivalence assessment of lidocaine PK parameters including AUClast, AUCinf, and Cmax are presented in **Tables 1** and **2** in the **Executive Summary**. Median (min, max) Tmax values were 13.9 (4.0, 18.0) h and 11.0 (4.0, 17.9) h for lidocaine patch 1.8% and Lidoderm patch 5%, respectively. The Cmax, AUCt and AUCinf for lidocaine patch 1.8% and Lidoderm patch 5% met the bioequivalent (BE) criteria. The point estimate of the geometric mean ratio (lidocaine patch 1.8%/Lidoderm patch 5%) for lidocaine Cmax, AUCt and AUCinf were 90.7%, 89.1%, and 88.6%, respectively. The corresponding 90% confidence intervals (CIs) were 85.0 – 96.8%, 84.9 – 93.5%, and 92.8 – 98.9%, respectively. All these 90% CIs fell within the 80 to 125% BE limit. Because three patches of lidocaine patch 1.8% showed equivalent lidocaine systemic exposure to three patches of Lidoderm patch 5%, the two products are considered PK bridged.

Figure 1 Mean Lidocaine Plasma Concentration (ng/mL) Time Profiles for Three Patches of Lidocaine Patch 1.8% (test) and Three Patches of Lidoderm Patch 5% (reference) Applied for 12 Hours (Study SCI-LIDO-PK-002A)



2.2 What are the effect of heat and exercise on lidocaine patch 1.8%?

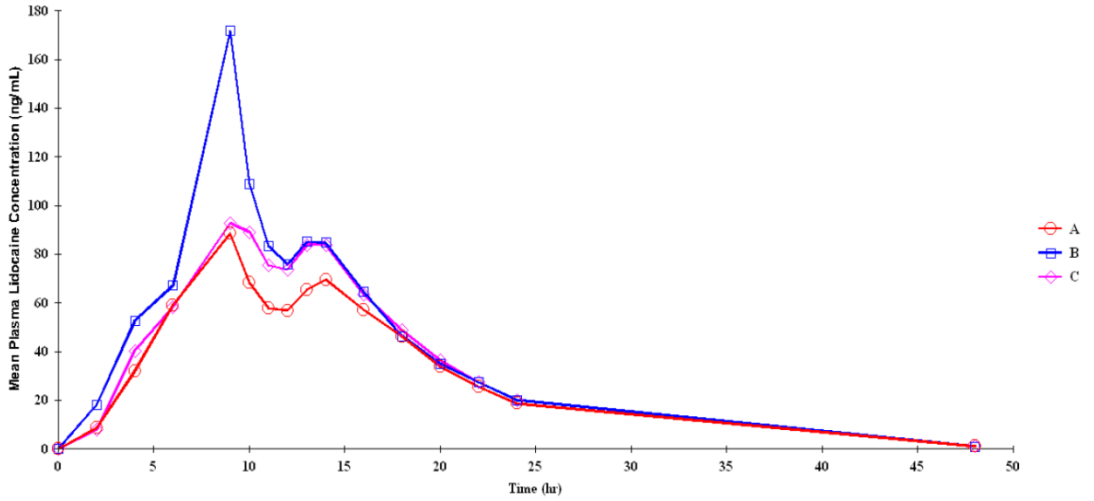
Use of heating pad on top of the lidocaine patches 1.8% immediately after patch application and at 8.50 hours post-application (heating pad was left in place for 20 min) increased lidocaine Cmax by 46% but did not affect the AUCt or AUCinf as compared to normal conditions. Moderate exercise (biking immediately after patch application and at 2.50, 5.50, and 8.50 hours post-patch application for 30 minutes) did not affect lidocaine PK. No tape reinforcement was used during the study.

In Study SCI-LIDO-HEX-001, the effect of heat and exercise was performed as a single dose, three-way cross-over design with three patches of lidocaine patch 1.8% applied to a defined area of normal skin on the back of each volunteer for a treatment duration of 12 hours under three conditions (i.e., moderate exercise [Treatment A], moderate heat [Treatment B], and normal conditions [Treatment C]). During Treatment A, subjects exercised on a bike for 30 minutes (target heart rate: 108 bpm) immediately after patch application and at 2.50, 5.50, and 8.50 hours post-patch application. During Treatment B, a standard 3-setting heating pad, used in accordance with the manufacturer's

instructions at a medium setting, was placed on top of the patch immediately after patch application and at 8.50 hours post-application. The heating pad was left in place for 20 minutes. A blanket/towel was placed between the patches and heating pad to reduce the chance of skin burning. No stress conditions were applied during Treatment C (normal conditions). There was a washout period of 7 days between treatments. Blood samples for PK determination were collected from each subject at pre-dose, and then at 2, 4, 6, 9, 10, 11, 12, 13, 14, 16, 18, 20, 22, 24, and 48 hours post-dose patch application.

The mean lidocaine plasma concentration-time profiles are shown in **Figure 2**. The PK results and statistical analysis results for equivalence assessment of lidocaine PK parameters including AUClast, AUCinf, and Cmax are presented in **Tables 3** and **4** in the **Executive Summary**. Use of heating pad on the patches increased lidocaine Cmax by 46% but did not affect the AUCt or AUCinf as compared to normal conditions. The point estimate of the geometric mean ratio (heating pad/normal condition) for lidocaine Cmax, AUCt and AUCinf were 146.57%, 108.02%, and 107.87%, respectively. The corresponding 90% confidence intervals (CIs) were 123.71 – 173.66%, 95.34 – 122.40%, and 95.46 – 121.79%, respectively. The 90% CIs for AUCt and AUCinf ratios fell within the 80 to 125% BE limit. Moderate exercise (biking immediately after patch application and at 2.50, 5.50, and 8.50 hours post-patch application for 30 minutes) did not affect lidocaine PK. The point estimate of the geometric mean ratio (exercise/normal condition) for lidocaine Cmax, AUCt and AUCinf were 95.14%, 90.25%, and 90.53%, respectively. The corresponding 90% confidence intervals (CIs) were 80.30 – 112.73%, 79.65 – 102.26%, and 80.15 – 102.25%, respectively.

Figure 2 Mean Lidocaine Plasma Concentration (ng/mL) Time Profiles for Three Patches of Lidocaine Patch 1.8% Applied for 12 Hours under Exercise (A), Heat (B) or Normal Condition (C) (Study SCI-LIDO-HEX-001)



In Study SCI-LIDO-PK-001 Cohort 2 submitted in the original submission, heat treatment with a heating pad was applied to each subject's back for 15 minutes on Day 1. Immediately after the heat treatment, 3 lidocaine patches 1.8% were applied to a defined area of normal skin on the subject's back which remained in place for 12 hours. On Day 8, the subjects completed an exercise regimen before the application of 3 lidocaine patches 1.8%. The subjects walked at a moderate pace on a treadmill for approximately 20 minutes. Approximately 5 minutes after completing the exercise, 3 lidocaine patches 1.8% were then applied for 12 hours to a defined area of normal skin on the back of the subjects. On Day 15, subjects had 3 lidocaine patches 1.8% applied to a defined area of normal skin on the back. The patches were reinforced with tape. Blood samples for PK were collected from each subject at pre-dose, and 2, 4, 6, 9, 10, 11, 12, 13, 14, 16, 18, 20, 22, 24, and 48 hours post-dose patch application.

Moderate heat (15 min heating pad immediately prior to patch application) and moderate exercise (walking at a moderate pace on a treadmill for approximately 20 minutes beginning approximately 30 minutes prior to the application) engaged prior to patch administration did not affect systemic lidocaine concentrations as compared to a normal patch application (**Table 5** in **Executive Summary**).

2.3 Is the bioanalytical assay adequately validated?

The bioanalytical LC/MS/MS method for the determination of lidocaine in human plasma was adequately validated. The assay precision and accuracy of the analytical method are summarized in **Table 6**.

Table 6 Lidocaine Assay Precision and Accuracy

	Study SCI-LIDO-PK-002A	Study SCI-LIDO-HEX-001
Nominal range for the calibration curve	0.200 to 300 ng/mL	0.200 to 200 ng/mL
LLOQ	0.2 ng/mL	0.2 ng/mL
QC	0.6, 15, 150, and 225 ng/mL	0.6, 10, 90, and 150 ng/mL
Precision (%CV)	3.36 to 17.6%	2.1 to 2.8%
Accuracy (% difference from theoretical)	-1.80 to 4.52%	3.3 to 4.7%

3 Labeling Recommendations

Labeling comments are shown below (reviewer's recommended additions are shown in blue and deletion in red):

Under Section **Dosage and Administration**

Do not apply external heat sources, such as (b) (4) heating pads or electric blankets (b) (4) directly to (b) (4) plasma lidocaine levels are increased (b) (4) can be applied after moderate heat exposure such as 15 min heating pad on a medium setting to the administration site (see WARNINGS AND PRECAUTIONS ((b) (4)) and CLINICAL PHARMACOLOGY (12.3)).

ZTlido may be used during moderate exercise such as biking for 30 minutes.

Because of the difference in bioavailability of ZTlido compared to Lidoderm® (lidocaine patch 5%), a different dosage strength is required to be administered to the patient. One ZTlido (lidocaine (b) (4) 1.8%) provides equivalent lidocaine exposure to one Lidoderm® (lidocaine patch 5%).

(b) (4)

Under Section **12.3 Pharmacokinetics**

ZTlido has different bioavailability compared to Lidoderm®. In a single-dose, crossover study conducted in 53 healthy volunteers, ZTlido (lidocaine (b) (4) 1.8%) demonstrated (b) (4) equivalent exposure (AUC) and peak concentration (Cmax) of lidocaine to Lidoderm® (lidocaine patch 5%) (b) (4)

Absorption: The amount of lidocaine systemically absorbed from ZTlido is directly related to both the duration of application and the surface area over which it is applied. In a pharmacokinetic study, three ZTlido (b) (4) were applied over an area of 420 cm^2 of intact skin on the backs of normal healthy volunteers for 12 hours. Blood samples were drawn for determination of lidocaine concentration during the (b) (4) application and for 12 hours after removal of (b) (4). The results are summarized in **Table 1**.

Table 1 Mean ± SD Absorption of lidocaine from ZTlido Normal volunteers (n = 53 (b) (4) 12-hour application time)

Table 1
Mean ± SD Absorption of lidocaine from ZTlido
Normal volunteers (n = 53 (b) (4) 12-hour application time)

(b) (4)	Application Site	Area (cm^2)	(b) (4)	C_{max} (ng/mL)	T_{max} (hr)*
3 (b) (4) of ZTlido (108 mg)	Back	420		(b) (4) 75.1 ± 28.0 (b) (4)	(b) (4) 13.9 (4.0, 18.0)

*median (min, max)

(b) (4)

Repeated application of three Lidoderm® patches simultaneously for 12 hours (recommended maximum daily dose), once per day for three days, indicated that the lidocaine concentration does not increase with daily use. The mean plasma pharmacokinetic profile for the 15 healthy volunteers is shown in Figure 1.

The pharmacokinetics of ZTlido (n=3 (b) (4)) was assessed in 12 healthy volunteers with exposure to external heat source (heating pad at medium setting applied for 20 minutes at Time 0 and 8.5 hours) or undergoing moderate exercise (cycling for 30 minutes at a heart rate of 108 bpm at Time 0, 2.5, 5.5 and 8.5 hours) and compared to pharmacokinetics of ZTlido at rest. Exposure to external heat results in increased peak plasma levels of (b) (4) lidocaine with a mean (SD) of 160.3 ± 100.1 ng/mL versus the peak plasma levels observed at rest (b) (4) with a mean (SD) of 97.6 ± 36.9 ng/mL. (b) (4) No clinically relevant differences in systemic absorption were observed under exercise conditions with a mean (SD) peak plasma concentrations (b) (4) of 90.5 ±

25.4 ng/mL. A separate study in 12 healthy volunteers showed that there was no effect on ZTlido pharmacokinetics when the (b) (4) is applied to the administration site after external heat exposure (heating pad at medium setting applied for 15 min prior to the (b) (4) application) or after engagement in exercise (walking at a moderate pace on a treadmill for approximately 20 minutes beginning approximately 30 minutes prior to the (b) (4) application).

[***Reviewer's comment**: Lidocaine patch 1.8% and Lidoderm® Patch 5% were shown to have equivalent systemic exposure of lidocaine in two studies (Studies SCI-LIDO-PK-001 with the use of tape and SCI-LIDO-PK-002A without the use of tape).* (b) (4) *Study SCI-LIDO-PK-002A included an apparent dose determination based on the amount of residual drug in used patches, skin, and envelopes/liners. The PK data from Study SCI-LIDO-PK-002A should be used because the patches were used according to the proposed labeling.*]

Distribution: When lidocaine is administered intravenously to healthy volunteers, the volume of distribution is 0.7 to 2.7 L/kg (mean 1.5 ± 0.6 SD, n = 15). At concentrations produced by application of ZTlido, lidocaine is approximately 70% bound to plasma proteins, primarily alpha-1-acid glycoprotein. At much higher plasma concentrations (1 to 4 µg/mL of free base), the plasma protein binding of lidocaine is concentration dependent. Lidocaine crosses the placental and blood brain barriers, presumably by passive diffusion.
*[**Reviewer's comment**: the proposed wording in Elimination is the same as Lidoderm, it is acceptable].*

Metabolism: It is not known if lidocaine is metabolized in the skin. Lidocaine is metabolized rapidly by the liver to a number of metabolites, including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacologic activity similar to, but less potent than that of lidocaine. A minor metabolite, 2,6-xylidine, has unknown pharmacologic activity. The blood concentration of

this metabolite is negligible following application of ZTlido. Following intravenous administration, MEGX and GX concentrations in serum range from 11 to 36% and from 5 to 11% of lidocaine concentrations, respectively.
[***Reviewer's comment**: "but is carcinogenic in rats" in the Lidoderm labeling was removed from the proposed labeling for ZTlido (input from pharma/tox)*].

(b) (4)**:** Lidocaine and its metabolites are excreted by the kidneys. Less than 10% of lidocaine is excreted unchanged. The half-life of lidocaine elimination from the plasma following IV administration is 81 to 149 minutes (mean 107 ± 22 SD, n = 15). The systemic clearance is 0.33 to 0.90 L/minute (mean 0.64 ± 0.18 SD, n = 15).
*[**Reviewer's comment**: the proposed wording in Elimination is the same as Lidoderm, it is acceptable].*

4 Appendix

4.1 Filing Memo

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	207-962 Resubmission	Proposed Brand Name	ZTlido Patch
OCP Division (I, II, III, IV, V)	II	Generic Name	Lidocaine patch 1.8%
Medical Division	DAAAP	Drug Class	Amide-type local anesthetic agent
OCP Reviewer	Wei Qiu, Ph.D.	Indication(s)	Relief of pain associated with post-herpetic neuralgia
OCP Team Leader	Yun Xu, Ph.D.	Dosage Form, Strength	Topical patch, 1.8%
Pharmacometrics Reviewer	N/A	Dosing Regimen	Up to 3 patches for up to 12 hours in a 24-hour period (12 hours on and 12 hours off)
Date of Submission	August 28, 2017	Route of Administration	topical
Primary Review Goal Date (GRMP)	February 4, 2018	Sponsor	Scilex Pharmaceuticals, Inc
		Priority Classification	Standard
PDUFA Due Date	February 28, 2018	Relevant INDs	IND 111537

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	3		SCI-LIDO-PK-002A, SCI-LIDO-PK-002B, SCI-LIDO-HEX-001
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 1:				
Phase 2:				
Phase 3:				
PK/PD -				

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	(3)		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			√	Sponsor stated that a 1.8% lidocaine patch with the commercial adhesive formulation demonstrated BE to Lidoderm® patch 5% in the pivotal study SCI-LIDO-PK-002A.
2	Has the applicant provided metabolism and drug-drug interaction information?			√	No new findings in the proposed label.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	√			Comparative BA study was conducted with the list drug Lidoderm 5% patch
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	√			
5	Has a rationale for dose selection been submitted?			√	Match the exposure of the list drug
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	√			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	√			

8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	√			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	√			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			√	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	√			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			√	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			√	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			√	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			√	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			√	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	√			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	√			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			√	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES

This NDA is fileable from clinical pharmacology perspective.

OSI inspection was requested for the pivotal comparative BA study on September 12, 2017. The requested OSI review due date is January 15, 2018.

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There is no potential review issue to be included in the 74-day letter.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

Background:

In response to the Complete Response Letter (CRL) issued on May 10, 2016, Scilex Pharmaceuticals Inc. resubmitted a 505(b)(2) NDA 207-962 for ZTlido Patch (lidocaine patch 1.8%) for the relief of pain associated with post-herpetic neuralgia on August 28, 2017.

The clinical pharmacology deficiency stated in the CRL is "The comparative bioavailability study, SCI-LIDO-PK-001, intended to bridge to the Agency's previous findings of efficacy and safety for Lidoderm patch 5%, cannot be used to establish bioequivalence because surgical tape was used to secure the Lidoderm 5%patches, and adequate evidence was not provided to justify that the use of tape would not affect lidocaine absorption from Lidoderm patch 5%". To address this deficiency, the sponsor was recommended to conduct a new adequately-designed comparative bioavailability study to demonstrate equivalent systemic exposure to Lidoderm patch 5%. The list drug product, Lidoderm patch 5%, must be used according to the approved package insert (e.g., without use of an overlay or tape). In this resubmission, the sponsor submitted Study SCI-LIDO-PK-002A which was performed without tape reinforcement on test or reference product. The sponsor stated that because Study SCILIDO-PK-002A is performed consistent with the intended label relative to tape reinforcement for both products (i.e., both excluded tape reinforcement), it is considered the "pivotal" study confirming bioequivalence between lidocaine patch 1.8% and Lidoderm® Patch 5%.

In addition, the sponsor mentioned that a market application is also intended to be submitted in the EU and Study SCI-LIDO-PK-002B was performed to establish bioequivalence between lidocaine patch 1.8% and Versatis® (lidocaine medicated plaster 5%), which is the approved EU trade name for Lidoderm® Patch 5%. As claimed by the European Union (EU) sponsor, Lidoderm® Patch 5% and Versatis® Medicated Plaster 5% are the same product (Versatis®

EPAR); therefore, the sponsor claimed that these data provide further confirmation of comparable bioavailability between lidocaine patch 1.8% and the listed drug.

Effects of heat and exercise were assessed in Study SCI-LIDO-HEX-001 where heat or exercises were applied while the subjects were wearing the patches. The sponsor concluded that, while moderate exercise has no clinically significant effect on drug absorption from the patches, local heating can result in a temporary increase in drug absorption.

Please find the filing slides for more details.

NDA 207962:
ZTlido Patch (Lidocaine patch 1.8%)

Resubmission

- **Sponsor:** Scilex Pharmaceuticals Inc.
- Dosage form: Topical patch
- 505(b)(2) NDA
- Indication: for relief of pain associated with post-herpetic neuralgia (PHN)
- Listed Drug:
  - Lidoderm® Patch, 5%

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Clin Pharm Deficiency in CR Letter (5/10/16)

4. The comparative bioavailability study, SCI-LIDO-PK-001, intended to bridge to the Agency's previous findings of efficacy and safety for Lidoderm patch 5%, cannot be used to establish bioequivalence because surgical tape was used to secure the Lidoderm 5% patches, and adequate evidence was not provided to justify that the use of tape would not affect lidocaine absorption from Lidoderm patch 5%.

   To address this deficiency, conduct a new adequately-designed comparative bioavailability study to demonstrate equivalent systemic exposure to Lidoderm patch 5%. The list drug product, Lidoderm patch 5%, must be used according to the approved package insert (e.g., without use of an overlay or tape).

   Additional data from Study SCI-LIDO-HEX-001 submitted during the review cycle were not reviewed. You may reference the submission as part of your response to the deficiencies cited in this letter.

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Study Number	Study Medication/Lot Number	Study Title
SCI-LIDO-PK-001	Lidocaine patch 1.8% / LIDT187 Lidoderm® Patch 5% / 23048 and 23018 Lidocaine IV / 35-459-DK	Phase 1, Randomized, Comparative Pharmacokinetic Study of Bolus Intravenous Lidocaine 0.7 mg/kg, Lidocaine Patch 1.8%, and Lidocaine Patch 5% (Lidoderm®) in Healthy Subjects and an Evaluation on the Effects of Heat and Exercise on the Pharmacokinetics of Lidocaine Patch 1.8% in Healthy Subjects
SCI-LIDO-PK-002A (Pivotal study-US)	Lidocaine patch 1.8% / 21510A Lidoderm® Patch 5% / 85248	Phase 1, Randomized Comparative Pharmacokinetic Study of Lidocaine Patch 1.8% (ZTlido™) and Lidocaine Patch 5% (Lidoderm®) in Healthy Subjects
SCI-LIDO-PK-002B (Pivotal study-EU)	Lidocaine patch 1.8% / 21510A Versatis® Medicated Plaster 5% / 85248	Phase 1, Randomized Comparative Pharmacokinetic Study of Lidocaine Medicated Plaster 1.8% (ZTlido™) and Lidocaine Medicated Plaster 5% (Versatis®) in Healthy Subjects[1]
SCI-LIDO-HEX-001	Lidocaine patch 1.8% / LIDT187	Phase 1, Open-Label, Randomized, Three-Treatment, Three-Sequence, Three-Period, Cross-over, Pharmacokinetic and Adhesion Performance Study of Lidocaine Patch 1.8% (36 mg) (3 patches) in Fasting, Healthy, Adult Human Subjects with Physical Exercise, Heat, and Normal Conditions

Comparative BA Study SCI-LIDO-PK-002A

- R, SD, comparative BA in healthy adult subjects
- Both lidocaine patch 1.8% and Lidoderm® Patch 5% administered as a single-dose three-patch application over a 12-hour dosing period with no tape reinforcement.
- PK sampling: pre-dose, and at 2, 4, 6, 9, 10, 11, 12, 13, 14, 16, 18, 20, 22, 24, and 48 hours post dose
- At the time of each PK blood draw, any part of the patch that was observed to be lifting may have been pressed down firmly (for not more than 10 seconds).

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Table 2.7.2.4 Mean Summary Descriptive Statistics for Lidocaine Pharmacokinetic Parameter Values for Healthy Subjects Following a Single-dose Application of Three Patches of Lidocaine Patch 1.8% and Lidoderm® Patch 5% for 12-Hour Duration (Study SCI-LIDO-PK-002A)

Pharmacokinetic Parameters	Lidocaine Patch 1.8% Mean ± SD (N=54)	Lidoderm® Patch 5% Mean ± SD (N=54)
C_{max} (ng/mL)	75.1 ± 28.0	86.6 ± 42.3
T_{max} (hr)	13.9 (4.0, 18.0)	11.0 (4.0, 17.9)
AUC_{0-t} (ng·hr/mL)	1242.9 ± 432.5	1420.8 ± 586.0
$AUC_{0-\infty}$ (ng·hr/mL)	1253.7 ± 432.5	1435.5 ± 588.9*
$T_{½}$ (hr)	5.4 ± 1.0	6.2 ± 1.6*

Table 2.5.4 Summary of Geometric Means and Bioequivalence Analyses for Lidocaine Patch 1.8% and Lidoderm® Patch 5% Patch (Study SCI-LIDO-PK-002A)

Pharmacokinetic Parameter	Geometric Mean		Ratio of Geometric Means	90% CI	
	Lidocaine Patch 1.8%	Lidoderm® Patch 5%		Lower	Upper
C_{max} (ng/mL)	70.6	78.1	90.7	85.0	96.8
AUC_{0-t} (ng·hr/mL)	1173.0	1320.6	89.1	84.9	93.5
AUC_{0-inf} (ng·hr/mL)	1184.4	1335.8	88.6	84.4	93.0

Heat and Exercise Study HEX-001

- R, SD, effect of heat and exercise
- Treatment: three Lidocaine Patches applied to the mid-lower back and worn for 12 hours
  - **A**: 30 min physical exercise at 2.50, 5.50 and 8.50 hours post-patch application
  - **B**:Heat was applied for 20 minutes after patch application, and for 20 minutes starting at 8.5 h after patch application
  - **C**: normal conditions.
- PK sampling: up to 48 h post dose

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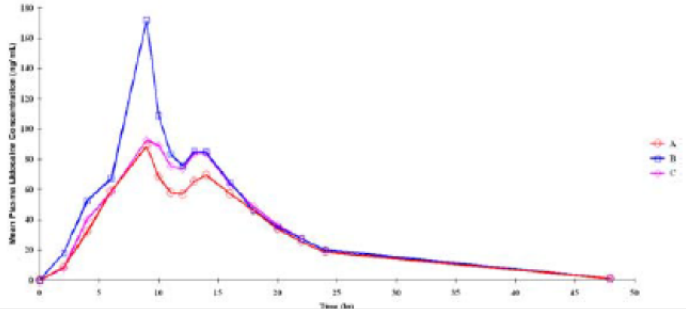
Effects of Heat and Exercise (Study HEX-001)



Statistics		C_{max} (ng/mL)	AUC_{0-tau} (ng·h/mL)	AUC_{0-inf} (ng·h/mL)	AUC% Extrapolation	T_{max}* (hr)	K_e (hr^{-1})	$T_{1/2}$ (hr)
Treatment A (Exercise)	N	12	12	12	12	12	12	12
	Mean	90.5	1328.8	1344.1	1.36	9.00	0.13	5.60
	SD	25.4	461.7	458.2	2.21	9.00-18.00	0.02	1.11
	CV (%)	28.1	34.7	34.1	162.3	30.0	18.9	19.9
Treatment B (Heat)	N	12	12	12	12	12	12	12
	Mean	160.3	1718.7	1731.3	0.90	9.00	0.14	5.39
	SD	100.0	1004.0	1005.0	1.11	9.00-16.05	0.03	1.34
	CV (%)	62.4	58.4	58.1	124.0	21.2	21.5	24.8
Treatment C (Normal)	N	12	12	12	12	12	12	12
	Mean	97.6	1487.4	1501.1	1.07	11.59	0.14	5.23
	SD	36.9	590.0	588.4	1.53	9.00-14.00	0.03	1.20
	CV (%)	37.8	39.7	39.2	143.2	18.9	21.5	23.0

Recommendation

- Filable from clin pharm perspective
  - Sponsor stated that a 1.8% lidocaine patch with the commercial adhesive formulation demonstrated BE to Lidoderm® patch 5%
  - Bioanalytical reports and datasets of PK raw data and parameters for all studies (PK-002A, PK-002B, and HEX-001) are included.
- Requested OSI inspection review for the pivotal BA study PK-002A by Jan 15, 2018.

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4.2 Study Synopsis

4.2.1 Study SCI-LIDO-PK-002A

Lidocaine Patch 1.8%

CSR P1980216A
SCI-LIDO-PK-002A

SPONSOR: Scilex Pharmaceuticals Inc. 9380 Judicial Drive San Diego, CA 92121	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER**	*(For National Authority Use Only)*
NAME OF FINISHED PRODUCT: ZTlido™	**VOLUME:**	
NAME OF ACTIVE INGREDIENT: Lidocaine	**PAGE:**	

STUDY TITLE:

Phase 1, Randomized Comparative Pharmacokinetic Study of Lidocaine Patch 1.8% (ZTlido™) and Lidocaine Patch 5% (Lidoderm®) in Healthy Subjects

INVESTIGATOR(S):

Phillip J. LaStella, MD

STUDY CENTER(S):

TKL Research, Inc.
One Promenade Boulevard, Suite 1101/1201
Fair Lawn, NJ 07410

PUBLICATION REFERENCE:

Lidoderm® Package Insert
Versatis® SmPC
FDA Draft Guidance for Industry, June 2016. Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs

STUDY PERIOD:

28 September 2016 – 27 October 2016

STUDY PHASE:

Phase 1

OBJECTIVES:

Primary Objectives

The primary objectives of this study were to characterize and compare the single-dose pharmacokinetics of ZTlido™ (investigational product / test) versus Lidoderm® (lidocaine patch

5%, reference product), and to determine the apparent dose (e.g., residual drug patch analysis / D).

Secondary Objectives

The secondary objectives of this study were as follows:

- To evaluate bioequivalence between ZTlido™ (lidocaine patch 1.8%) and Lidoderm® (lidocaine patch 5%).
- To evaluate and compare the safety following a single dose of the investigational product (ZTlido™) and the comparator product. Lidoderm®.
- To evaluate skin irritation of ZTlido™ and Lidoderm®.
- To establish swabbing procedures for residual drug on liners and envelopes (ZTlido™ and Lidoderm®) and liners (Versatis®) after removal of patch from the envelopes and removal of liners prior to application of the patch.
- To establish skin swabbing procedures for residual drug once patches are removed for ZTlido™ and Lidoderm®/Versatis® (performed in Lead-in Portion).

METHODOLOGY:

Lead-in Portion

The Lead-in portion was a single-center study in healthy adult subjects. Subjects were screened to determine eligibility up to 28 days before beginning study treatment. Subjects received either three ZTlido™, Lidoderm®, or Versatis® patches for 12 hours to a defined area of normal skin on the back. Patch envelopes (ZTlido™ and Lidoderm®) were swabbed for residual lidocaine after patch removal. Patch liners (all three products) were swabbed for residual lidocaine. The swab samples were sent to [redacted] (b) (4) for residual drug analysis. The results established the skin, envelope, and liner swabbing procedures used during the Pharmacokinetic (PK) Portion of this study and Study SCI-LIDO-PK-002B (comparative PK ZTlido™ versus Versatis®).

PK Portion

The study was a single-center, randomized, comparative PK study conducted in healthy adult subjects. Subjects were screened to determine eligibility up to 28 days before beginning study treatment. Subjects were randomized to one of two treatment sequences.

On Day -1 (Period 1) and Day 7 (Period 2), subjects checked into the clinic site. On Day 1 (Period 1) and Day 8 (Period 2), TKL personnel applied either 3 ZTlido™ or Lidoderm® (dependent on each subject's randomization scheme) for 12 hours to a defined area of normal skin on the back. During Periods 1 and 2, patches were evaluated for degree of adhesion by the trained scorer using the FDA recommended rating scale. During Periods 1 and 2 serial PK samples were collected for the determination of lidocaine plasma concentration at (pre-dose / Time 0) and at scheduled time points up to 48 hours (Day 3 [Period 1] and Day 10 [Period 2]) following the patch application. At the time of each PK blood draw, any part of the patch that

was observed to be lifting may have been pressed down firmly (for not more than 10 seconds). All subjects completed a 7-day washout period following Period 1 and Period 2.

Safety and tolerability were evaluated by monitoring the occurrence of AEs, local tolerability, changes in abbreviated physical examination findings, ECGs, vital signs (blood pressure and pulse rate) measurements, and clinical laboratory test results (biochemistry, hematology).

Skin irritation was evaluated at the site of application after patch removal. Once skin irritation was assessed, all patched areas were swabbed as per detailed instruction provided in the Laboratory Manual for PK Patch and Swab Sample Collection and Processing by (b) (4).

NUMBER OF SUBJECTS (PLANNED, ENROLLED, AND ANALYZED):

Lead-In Portion

A total of 36 subjects (12 subjects per ZTlido™, Lidoderm®, and Versatis®) were enrolled in the study.

PK Portion

A total of 54 subjects (separate from the Lead-In portion) were randomized to this study; 28 subjects were randomized to Sequence 1 and 26 subjects were randomized to Sequence 2. Subjects in Sequence 1 received ZTlido™ in Period 1 and Lidoderm® in Period 2. Subjects in Sequence 2 received Lidoderm® in Period 1 and ZTlido™ in Period 2. All subjects (100%) in both Sequence 1 and Sequence 2 completed the study

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Subjects to be included in this study were those who:

1. Were healthy subjects (confirmed by medical history, laboratory work, and physical exam);
2. Were males and females ≥ 18 years of age;
3. If of childbearing potential, were using an acceptable form of birth control (i.e., non-hormonal intra-uterine device [IUD], diaphragm, condom, bilateral tubal ligation, abstinence, or were in a monogamous relationship with a partner who has had a vasectomy);
4. In the case of females of childbearing potential, had a negative serum pregnancy test (SPT) at Screening and a negative UPT at Study Day -1, (a woman was considered to be of childbearing potential unless she was postmenopausal for at least 12 months or was surgically sterile [hysterectomy, bilateral oophorectomy]);
5. Had clinical lab tests (hematology and chemistry) and vital signs within normal limits, or assessed by the investigator as not of clinical significance;
6. Were able to read, understand, and provide signed informed consent (IC); and
7. Were willing to participate in Study SCI-LIDO-PK-002B.

The eligibility criteria were the same for the Lead-In portion except for an upper age limit (≤ 65 years of age); had to be free of any systemic or dermatologic disorders; and were of any skin type or race that would not allow discernment of erythema.

STUDY DRUG, DOSE, AND MODE OF ADMINISTRATION, BATCH/LOT NUMBER:

During the Lead-In Portion of the study, 12 subjects each were treated with ZTlido™, Lidoderm®, and Versatis®.

During the PK Portion of the study, 54 subjects were treated with ZTlido™ and 54 subjects were treated with the Lidoderm®.

Lidocaine Patch 1.8% (ZTlido™) (investigational product / test)

ZTlido™ was applied as 3 patches for 12 hours to a defined area of normal skin on the back of subjects. The lot number was 21510A.

DURATION OF TREATMENT:

Lead-In Portion

Each enrolled subject received 3 patches of either ZTlido™, Lidoderm®, or Versatis® for 12 hours.

PK Portion

Each enrolled subject received a total of 6 lidocaine patches. Subjects received 3 lidocaine patches, either ZTlido™ or Lidoderm® (dependent on each subject's randomization scheme) in Sequence 1 and 3 lidocaine patches, ZTlido™ or Lidoderm®, in Sequence 2, for 12 hours to a defined area of normal skin on the back.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH/LOT NUMBER:

The reference therapy was Lidoderm®. The lot number of the reference therapy used in this study was 85208 for the Lead-In and 85248 for the PK Portion.

The lot number of the Versatis® product used in the Lead-In was 250G01.

Lidocaine Patch 5% (Lidoderm®, reference product)

For the Lead-In and PK Portions, Lidoderm® was applied as 3 patches for 12 hours to a defined area of normal skin on the back of subjects. In the Lead-In, Versatis® was applied as 3 patches for 12 hours to a defined area of normal skin on the back of subjects.

Lidoderm® and Versatis® patches were manufactured by Teikoku Seiyaku Company for Endo Pharmaceuticals and Grünenthal GmbH, respectively.

CRITERIA FOR EVALUATION:

Efficacy:

Not applicable.

Safety:

Lead-In Portion

All AEs and SAEs were monitored and recorded during the time of the subject participated in this study.

PK Portion

All AEs and SAEs were monitored and recorded during the time the subject participated in this study. Skin irritation was evaluated at the site of application after patch removal. A serum pregnancy test (SPT) was conducted on women of child-bearing potential at Screening, and urine pregnancy tests (UPTs) were conducted at Day -1 and Day 7. Urine drug screens were conducted on all subjects at Screening, Day -1, and Day 7. Blood was taken at Screening for laboratory evaluations (hematology and chemistry). Normal ranges and values outside the normal ranges are identified by the central laboratory. A listing of all out-of-range laboratory test results at any assessment time point is also provided. Determination of clinical significance for all out-of-range laboratory values was made by each investigator and included in the listing.

The safety analysis variables were defined as follows:

- Adverse Events
- Clinical Laboratory Values (Hematology and Blood Chemistry)
- Vital Signs
- Physical Exam
- ECGs

STATISTICAL METHODS:

Data Set Descriptions:

Pharmacokinetic Concentration Population: All subjects who received at least one dose of lidocaine and who had plasma concentration data available were included in the Pharmacokinetic Concentration Population. This population was used for the presentation of the descriptive statistics for lidocaine concentration data and for the listing of PK parameters.

Pharmacokinetic Parameter Population: All subjects who were eligible for the Pharmacokinetic Concentration Population, who additionally provided PK parameters from both test and references were included in the Pharmacokinetic Parameter Population. This population was used for the primary statistical analysis and summary of PK parameters.

Safety Population: All subjects who received at least one dose of study medication were included in the Safety Population. The safety population was used for presentation of all demographic, disposition and safety data.

Plasma Pharmacokinetic Parameters

Parameter	Definition
C_{max}	Maximum observed plasma concentration
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from time 0 to time of the last measurable plasma concentration (T_{last}) calculated using the linear trapezoidal method.
$AUC_{(0-\infty)}$	Area under the plasma concentration-time curve from time 0 to infinity calculated as the sum of $AUC_{(0-t)}$ + (C_{last}/ke), where C_{last} was the last measurable plasma concentration and ke was the apparent terminal elimination rate constant.
T_{max}	Time point at which the maximum plasma concentration (C_{max}) was observed
$t_{½}$	Elimination half-life, calculated as ln(2)/ke. ke was the negative of the slope of the log-transformed concentrations vs time, determined by linear regression over the time points corresponding to the apparent elimination phase of the kinetics.
k_e	Elimination rate constant, derived from the slope of the decay of the log concentration over time. The lower and upper time points used for regression was determined through visual examination. A minimum of 3 time points after C_{max} was required for determination.
CL/F	apparent total body clearance $CL/F = \left(\frac{Dose}{AUC_{0-\infty}}\right)$ Note: Weight-adjusted CL/F (CL/F/kg) was also calculated.
V_D/F	apparent total volume of distribution, $V_D/F = \left(\frac{Dose}{\lambda_Z * AUC_{0-\infty}}\right)$
F_{rel}	$\frac{AUC_{test}}{AUC_{standard}} * \frac{Dose_{standard}}{Dose_{test}}$
D	Apparent dose, equal to the quantity of lidocaine in the 3 patches as manufactured (36 mg for the investigational product and 700 mg for the reference product) minus the quantity recovered from the used patch and adhesive residue.

All PK parameters are summarized by treatment period, using mean, standard deviation, 95% confidence interval, minimum, median, and maximum.

In addition, C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ were tested for bioequivalence between ZTlido™ and Lidoderm®. For this, the log-transformed quantities were analysed in a mixed effects analysis of

variance model, with treatment, sequence, and period as fixed effects and subject within sequence as a random effect. Estimates of the difference between treatment least squares means were obtained from the model with 90% confidence intervals. These estimates and confidence intervals were back-transformed on to the original scale to provide estimates of the geometric means for each treatment, and of the ratio of the geometric means. By convention, if the 90% confidence interval of the ratio of geometric means was within 80% to 125%, then the two treatments were considered bioequivalent.

Apparent dose (D / residual drug patch analysis) and relative bioavailability was compared between the test product and reference product using analysis of variance of the untransformed data; T_{max} and $t_{½}$ were compared pairwise among all treatments using Kruskal-Wallis methods.

Mean and individual subject plasma concentration time curves are presented on both linear and semilogarithmic scales.

Lead-In results are listed in Appendix 16.1.12. Lead-in results were not summarized for this report.

EFFICACY RESULTS:

Not applicable

SAFETY RESULTS:

Overall, there were 2 AEs among 2 subjects. One (1) subject receiving ZTlido™ and 1 subject receiving Lidoderm® reported AEs. The 2 AEs were mild in severity, not related to the study products, and did not lead to discontinuation of the subjects.

Additional safety measures included skin irritation assessments, an ECG, a physical exam, laboratory tests, vital signs, and pregnancy tests (UPT and SPT) for women of childbearing potential. There were no clinically significant findings in any of the additionally safety measures.

There were no AEs observed for any subject during the Lead-In portion of the study.

CONCLUSION:

This study was a Phase 1, randomized, comparative PK study of ZTlido™ and Lidoderm® in healthy adult subjects. Fifty-four (54) subjects who met the study entry criteria were randomized to either Sequence 1 (28 subjects) or Sequence 2 (26 subjects). Subjects in Sequence 1 received ZTlido™ on Day 1 of the study and Lidoderm® on Day 8. Subjects in Sequence 2 received Lidoderm® on Day 1 of the study and ZTlido™ on Day 8. All enrolled subjects completed the study.

The primary objective of this study was to characterize and compare the single-dose pharmacokinetics of ZTlido™ (investigational product/test) versus Lidoderm® and determine the apparent dose based on the residual drug analysis. The secondary objectives of this study were to evaluate the bioequivalence between ZTlido™ and Lidoderm®, the evaluate and compare the

safety following a single dose, to evaluate skin irritation, establish envelope/liner swabbing procedures, skin swabbing procedures for residual drug once patches were removed, and to compare residual drug analysis (envelope/liner, skin, and patches) between ZTlido™ and Lidoderm®.

Pharmacokinetic parameters were assessed by measuring lidocaine concentrations in the plasma at set time points. The mean plasma lidocaine concentrations increased during the application period reaching mean peak concentrations at 12.8 hours for ZTlido™ and 11.0 hours for Lidoderm®. Mean lidocaine concentrations for subjects receiving both ZTlido™ and Lidoderm® appeared to decrease slowly from 14 to 48 hours in a generally log-linear manner thereafter. The elimination constant (K_e) was calculated as 0.1326 for ZTlido™ and 0.1192 for Lidoderm®.

The following table presents the mean (±SD) of PK parameters for subjects receiving ZTlido™ and Lidoderm®. The mean relative bioavailability of ZTlido™ versus Lidoderm® was 6.63 (4.15).

Lidocaine Patch 1.8% **CSR P1980216A**
SCI-LIDO-PK-002A

PK Parameter	N	Mean (SD)	Geometric Mean	Median	Min, Max	95% CI
Lidocaine Patch 1.8% (ZTlido)						
Cmax (ng/mL)	54	75.1 (28.0)	70.6	68.6	27.4, 183.0	(67.4, 82.7)
Tmax (hr)	54	12.8 (2.9)	12.4	13.9	4.0, 18.0	(12.0, 13.6)
AUC0-t (ng*hr /mL)	54	1242.9 (432.5)	1173.0	1196.9	581.1, 2611.0	(1124.9, 1360.9)
AUC0- ∞ (ng*hr /mL)	54	1253.7 (432.5)	1184.4	1212.7	608.4, 2615.9	(1135.7, 1371.8)
T1/2 (hr)	54	5.4 (1.0)	5.3	5.3	3.0, 8.2	(5.1, 5.7)
Ke (hr-1)	54	0.1326 (0.0253)	0.1303	0.1308	0.0849, 0.2300	(0.1256, 0.1395)
Apparent Dose (mg)[1]	54	47.9 (8.8)	47.1	47.8	24.5, 65.1	(45.5, 50.3)
CL/F (L/h)	54	41.3 (12.1)	39.7	40.5	22.3, 77.1	--
Weight Adjusted CL/F (L/h/kg)	54	0.54 (0.18)	0.51	0.51	0.28, 1.10	--
VD/F (L)	54	316.7 (87.6)	304.8	314.2	146.7, 516.8	--
PK Parameter	**N**	**Mean (SD)**	**Geometric Mean**	**Median**	**Min, Max**	**95% CI**
Lidocaine Patch 5% (Lidoderm)						
Cmax (ng/mL)	54	86.6 (42.3)	78.1	75.1	26.2, 234.0	(75.1, 98.2)
Tmax (hr)	54	11.0 (2.0)	10.8	11.0	4.0, 17.9	(10.5, 11.6)
AUC0-t (ng*hr /mL)	54	1420.8 (586.0)	1320.6	1284.1	574.9, 3960.6	(1260.8, 1580.7)
AUC0- ∞ (ng*hr /mL)	53	1435.5 (588.9)	1335.8	1290.2	617.7, 3966.0	(1273.1, 1597.8)
T1/2 (hr)	53	6.2 (1.6)	6.0	5.7	3.6, 10.8	(5.7, 6.6)
Ke (hr-1)	53	0.1192 (0.0274)	0.1160	0.1220	0.0640, 0.1924	(0.1117, 0.1268)
Apparent Dose (mg)[1]	54	332.6 (144.1)	269.3	335.2	3.4, 652.7	(293.2, 371.9)
CL/F (L/h)	53	268.8 (175.3)	201.8	232.6	2.6, 890.7	--
Weight Adjusted CL/F (L/h/kg)	53	3.53 (2.44)	2.61	3.11	0.03, 13.64	--
VD/F (L)	53	2474.0 (2067.2)	1739.7	1896.7	31.3, 10248.1	--
Lidocaine 1.8% vs. Lidocaine 5%						
Relative Bioavailability	53	6.63 (4.15)	5.04	5.82	0.08, 20.03	--

Note: SD = Standard Deviation, CI = Confidence Interval.
[1] Calculated as the total quantity of lidocaine in the 3 patches as manufactured minus the total residual quantity recovered from the patches, skin, and envelopes/liners.

The topical application of ZTlido™ and Lidoderm® were safe. There were a total of 2 AEs among 2 subjects; both AEs were TEAEs. Both TEAEs were mild in severity and unrelated to the study drug. One subject reported a TEAE while receiving ZTlido™ and one subject reported a TEAE while receiving Lidoderm®. No subject was discontinued from the study due to an AE. There were a total of 94 protocol deviations among 54 subjects. The deviations were minor and did not impact the study results. No subject was discontinued from the study or excluded from analysis due to a protocol deviation. Skin irritation was measured using dermal response scores for each application site (after patch removal and prior to skin swabbing) on the application day. The dermal response score was either 0 (no irritation) or 1 (mild erythema, barely perceptible) for all patch assessments for both Lidoderm® and ZTlido™ with the exception of 2 subjects receiving the ZTlido™ patch. These two subjects had a score of 2 (definite erythema, readily visible; or minimal edema; or minimal papular response) at the first, second, and third skin patch application site.

Overall, PK bioequivalence was demonstrated between ZTlido™ and Lidoderm®. The pharmacological parameters C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ were assessed for non-inferiority. The 90% confidence interval of the ratio of geometric means for these plasma PK parameters was within 80% to 125%; therefore, the two treatments were considered bioequivalent. Adhesion non-inferiority was also demonstrated between ZTlido™ and Lidoderm®. ZTlido adhesion (mean score of 0.22) was also statistically superior to Lidoderm® (mean score of 0.86) at the 12-hour time point ($p<0.001$).

Fifty-four (54) subjects completed this Phase 1, randomized study to compare the single-dose pharmacokinetics of ZTlido™ and Lidoderm® to determine the apparent dose based on patch residual drug analysis (patch, skin and envelope/liner). Overall, the topical applications of ZTlido™ and Lidoderm® were safe. There were a total of 2 AEs among 2 subjects; all AEs were TEAEs. All TEAEs were mild in severity and unrelated to the study product. The mean plasma lidocaine concentrations increased during the application period reaching mean peak concentrations at 12.8 hours for ZTlido™ and 11.0 hours for Lidoderm®. Mean lidocaine concentrations for subjects receiving both ZTlido™ and Lidoderm® appeared to decrease slowly from 14 to 48 hours in a generally log-linear manner thereafter.

DATE OF FINAL REPORT:

June 29, 2017

2.0 SYNOPSIS

Name of Sponsor / Company: Scilex Pharmaceuticals, Inc. **Name of Finished Product:** **Test Product** Lidocaine Patch 36 mg (1.8%). **Name of Active Ingredients:** Lidocaine.	Individual study table referring to part of the dossier Volume: 01	(for national authority use only)

Title of Study: An open label, randomized, three-treatment, three-sequence, three-period, cross-over, pharmacokinetic and adhesion performance study of Scilex Pharmaceuticals, Inc., Lidocaine Patch 36 mg/patch (1.8%) (3 patches) in fasting, healthy, adult, human subjects, with physical exercise, heat and normal conditions.

Investigators:

Principal Investigator: John D. Peterson, Pharm.D, R.Ph.

Sub-Investigator : Dr. Patrick A.Luger, M.D, Mr. Brent Gillund, MA, CCRC, Dr. Nayan Patel, Bachelor of Science in Medicine, M.B.B.S.

(b) (4)

[redacted]

Study Center(s):

Clinical facility

AXIS Clinicals
1711 Center Avenue West
Dilworth, MN 56529-0675
Telephone No: 218-284-2950

AXIS USA clinical facility is spread across 35,000 sq ft on the east side of the 120,000 sq ft building. The clinic space is divided into 3 suites of 60 beds each (180 beds in total) and a 6,000 sq ft dermatology center with an independent access for easy participant throughput.

The clinical unit also includes a full license pharmacy with DEA license to handle and store controlled substances onsite, and a central processing lab. The screening section is designed in a unique single flow system for easy access and flow of volunteers.

Name of Sponsor / Company: Scilex Pharmaceuticals, Inc.	Individual study table referring to part of the dossier	(for national authority use only)
Name of Finished Product: **Test Product** Lidocaine Patch 36 mg (1.8%).		
Name of Active Ingredients: Lidocaine.	Volume: 01	

Clinical Laboratory Services:

(b) (4)

Waste Management:

(b) (4)

Name of Sponsor / Company: Scilex Pharmaceuticals, Inc.	Individual study table referring to part of the dossier Volume: 01	(for national authority use only)
Name of Finished Product: **Test Product** Lidocaine Patch 36 mg (1.8%).		
Name of Active Ingredients: Lidocaine.		

Medical Writing and Statistical Services:

(b) (4)

Pharmacokinetic Services:

(b) (4)

Bioanalytical Laboratory:

(b) (4)

Name of Sponsor / Company: Scilex Pharmaceuticals, Inc.	Individual study table referring to part of the dossier	(for national authority use only)
Name of Finished Product: **Test Product** Lidocaine Patch 36 mg (1.8%).		
Name of Active Ingredients: Lidocaine.	Volume: 01	

(b) (4)

Publication (Reference): Not applicable (no publication has been issued based on the results of the study).

Study period	**Phase of development:**
Date of first enrollment: 08JAN16. **Date of completion:** 25JAN16. **Start date of analysis:** 02FEB16. **End date of analysis**: 05FEB16.	Pharmacokinetic and adhesion performance study (Phase-I).

Name of Sponsor / Company: Scilex Pharmaceuticals, Inc. **Name of Finished Product:** **Test Product** Lidocaine Patch 36 mg (1.8%). **Name of Active Ingredients:** Lidocaine.	Individual study table referring to part of the dossier Volume: 01	(for national authority use only)

Objectives:

Primary Objective:

The objectives of this study are to evaluate the pharmacokinetic and adhesion performance of ZTlido, Scilex Pharmaceuticals, Inc., Lidocaine Patch 36 mg/Patch (1.8% × 3 patches), in fasting with physical exercise, heat and normal conditions.

Secondary Objective:

To monitor the adverse events and to ensure the safety of the subjects.

Methodology: An open label, randomized, three-treatment, three-sequence, three-period, cross-over, pharmacokinetic and adhesion performance study in healthy, adult, human subjects under fasting, with physical exercise, heating and normal conditions.

Calculation of pharmacokinetic parameters were done for Lidocaine 36 mg (1.8%) drug concentration time data using WinNonlin professional software Version 5.0.1 (Pharsight Corporation, USA) by non-compartmental method. Statistical comparison of the pharmacokinetic parameters and adhesion scores of the three treatments was carried out using General Linear Model (PROC GLM) of SAS® Release 9.4 (SAS Institute Inc., USA) to evaluate the pharmacokinetic and adhesion performance of ZTlido, Scilex Pharmaceuticals, Inc., Lidocaine Patch 36 mg/Patch (1.8% × 3 patches). Descriptive statistics was computed and reported for primary and secondary pharmacokinetic parameters of Lidocaine 36 mg (1.8%).

Adhesion Analysis included all patches from 12 subjects and no patches fell off during the study or removed early for unacceptable irritation or dropped out of the study before the end of the 12-hour application. *(Refer table 07 for Individual Adhesion scores at each assessment time point for all subjects).*

Adhesion analysis for Lidocaine 36 mg (1.8%) was performed using SAS® Release 9.4 (SAS Institute Inc., USA).

Name of Sponsor / Company: Scilex Pharmaceuticals, Inc. **Name of Finished Product:** **Test Product** Lidocaine Patch 36 mg (1.8%). **Name of Active Ingredients:** Lidocaine.	Individual study table referring to part of the dossier Volume: 01	(for national authority use only)

Number of subjects (planned and analyzed):
Planned for inclusion: 12 (01-12).
Included subjects: 12 (01- 12) + 08 standby subjects.
Completed subjects: 12 (01-12).
Drop-out / withdrawn: Not Applicable.
Included subjects for bioanalysis: 12 (01-12).
Included subjects for pharmacokinetic analysis: 12 (01-12).
Included subjects for statistical analysis: 12 (01-12).
Included subjects for Adhesion Analysis: 12 (01-12).

Demographic profile of subjects participated in the study:

Total number of subjects enrolled (N)=12				
	Age (years)	**Height (m)**	**Weight (kg)**	**BMI (kg/m^2)**
RANGE	19 - 62	1.509 – 1.802	58.10 – 99.85	21.95 – 30.97
MEAN	46.17	1.66	76.95	27.81
SD	15.94	0.09	12.80	2.91
% CV	34.5	5.4	16.6	10.4

Diagnosis and main criteria for inclusion:
Volunteers aged 18 years and older with a body mass index (BMI) of 18.00 to 32.49 kg/m^2 were to be selected according to the inclusion and exclusion criteria. They were assessed to be in healthy condition based on demographic data including sex, date of birth, height, weight, BMI, history of smoking, history of intake of abusive/recreational drugs, history of alcohol consumption, history of blood donation, history of participation in a drug research study, pre-study medical history including medications, allergies, health history, physical examination including vital signs (completed at screening or check-in), normal laboratory test results [hematology, biochemistry, urinalysis, including negative HIV 1 & 2, HBsAg, HCV tests] and 12-lead ECG.

Name of Sponsor / Company: Scilex Pharmaceuticals, Inc. **Name of Finished Product:** **Test Product** Lidocaine Patch 36 mg (1.8%). **Name of Active Ingredients:** Lidocaine.	Individual study table referring to part of the dossier Volume: 01	(for national authority use only)

Treatment (A), dose, mode of administration and batch number:

Treatment (A): Lidocaine Patches 36 mg (1.8%), with physical exercise conditions.

Dose: 3× 36 mg/Patch (1.8%).

Mode of administration: After an overnight fast of at least 10 hours, three Lidocaine Patches 36 mg (1.8%) of Treatment (A) was applied to the mid-lower back condition according to randomization schedule and worn for the 12 hours in study period.

Lot No.: LIDT187.

Treatment (B), dose, mode of administration and batch number:

Treatment (B): Lidocaine Patches 36 mg (1.8%), with heating conditions.

Dose: 3× 36 mg/Patch (1.8%).

Mode of administration: After an overnight fast of at least 10 hours, three Lidocaine Patches 36 mg (1.8%) of Treatment (B) was applied to the mid-lower back according to randomization schedule and worn for the 12 hours in study period. Heat was applied for 20 minutes after patch application, and for 20 minutes starting at 8.5 h after patch application.

Lot No.: LIDT187.

Treatment (C), dose, mode of administration and batch number:

Treatment (C): Lidocaine Patches 36 mg (1.8%), with normal conditions.

Dose: 3× 36 mg/Patch (1.8%).

Mode of administration: After an overnight fast of at least 10 hours, three Lidocaine Patches 36 mg (1.8%) of Treatment (C) was applied to the mid-lower back according to randomization schedule and worn for the 12 hours in study period.

Lot No.: LIDT187.

Name of Sponsor / Company: Scilex Pharmaceuticals, Inc. **Name of Finished Product:** **Test Product** Lidocaine Patch 36 mg (1.8%). **Name of Active Ingredients:** Lidocaine.	Individual study table referring to part of the dossier Volume: 01	(for national authority use only)

Duration of treatment:

Treatment periods:

Period-I: 09JAN16.

Period-II: 16JAN16.

Period-III: 23JAN16.

Wash-out period: A washout period of 7 days was maintained between each treatment schedule.

Criteria for Evaluation:

Efficacy evaluations:

The venous blood samples (1 x 6 mL) were collected in pre-labelled vacutainer tubes containing K_2EDTA during each period.

A total of 16 blood samples (each 6 mL) in each period were collected in pre-labelled vacutainer tubes containing K_2EDTA during each period.

A pre-dose blood sample (0.00 hr) of 6 mL was collected within one hour before patch application in each period.

The post dose blood samples of 6 mL were collected at, 2.00, 4.00, 6.00, 9.00, 10.00, 11.00, 12.00, 13.00, 14.00, 16.00, 18.00, 20.00, 22.00, 24.00 and 48.00 hours in each period.

Skin Irritation Assessment:

Skin irritation was evaluated at the site of application: at Pre-application (0 hour) [within 30 minutes before patch application], 30 minutes (with a window period ±10 minutes) post patch removal and at 2 hrs post patch removal with a window period of ±15 minutes.

Observed skin reaction was scored according to the following two scales:

Name of Sponsor / Company: Scilex Pharmaceuticals, Inc. **Name of Finished Product:** **Test Product** Lidocaine Patch 36 mg (1.8%). **Name of Active Ingredients:** Lidocaine.	Individual study table referring to part of the dossier Volume: 01	(for national authority use only)

Scale 1: Dermal Response:

Skin Appearance	Score
No evidence of irritation	0
Minimal erythema, barely perceptible	1
Definite erythema, readily visible; or minimal edema; or minimal papular response	2
Erythema and papules	3
Definite edema	4
Erythema, edema, and papules	5
Vesicular eruption	6
Strong reaction spreading beyond test (i.e., application) site	7

Scale 2: Other Effects

Observation	Score (Numeric equivalent)
Slightly glazed appearance	A (0)
Marked glazed appearance	B (1)
Glazing with peeling and cracking	C (2)
Glazing with fissures	F (3)
Film of dried serous exudates covering all or part of the patch site	G (3)
Small petechial erosions and/or scabs	H (3)

(Refer table no.02, 03, 04 and 05 for individual skin irritation scores for all subjects, Overall Descriptive Statistics of Irritation Scores for Treatment A (with physical exercise), Treatment B (with heating) and Treatment C (under normal conditions) at 12.5 and 14 hours respectively.)

Name of Sponsor / Company: Scilex Pharmaceuticals, Inc.	Individual study table referring to part of the dossier Volume: 01	(for national authority use only)
Name of Finished Product: **Test Product** Lidocaine Patch 36 mg (1.8%).		
Name of Active Ingredients: Lidocaine.		

Adhesion Assessments:

Adhesion assessment was done immediately after application (0 hour) and at 0.50, 3.00, 6.00, 9.00 and 12.00 (before patch removal) hours after application with a window period ±15 minutes.

The patch was checked for degree of adhesion by the trained scorer using the FDA recommended rating scale.

0	=	≥ 90% Adhered (essentially no lift off the skin)
1	=	≥ 75% to < 90% Adhered (some edges only lifting off the skin)
2	=	≥ 50% to < 75% Adhered (less than half of the patch lifting off the skin)
3	=	> 0% to < 50% Adhered but not detached (more than half of the patch lifting off the skin without falling off)
4	=	0% Adhered - patch detached (patch completely off the skin)

(Refer table 07 for Individual Adhesion scores at each assessment time point for all subjects.

Safety evaluations:

Detailed medical examination including medical history, physical examination, vital signs, clinical laboratory tests, and 12-lead ECG were carried out at the time of screening to exclude any clinically significant medical condition that may interfere or likely to interfere with the pharmacokinetics of the drug. Safety assessments were carried out at the time of check-in and throughout the study.

Urine drug screen, alcohol breath analysis and pregnancy test (females only) was carried out at screening and at the time of each period check-in.

Complete vital signs monitoring (blood pressure, pulse rate, temperature and respiratory rate) were conducted in a sitting position before patch application. Vital signs (blood pressure, respiratory rate and pulse rate) were conducted at 4, 10 and 24 hours after patch application in a sitting position and at the ambulatory visit.

Name of Sponsor / Company: Scilex Pharmaceuticals, Inc.	Individual study table referring to part of the dossier	(for national authority use only)
Name of Finished Product: **Test Product** Lidocaine Patch 36 mg (1.8%).		
Name of Active Ingredients: Lidocaine.	Volume: 01	

All in-house and ambulatory vital sign monitoring was done with a window period of ± 30 minutes to the scheduled time except pre-patch application vitals which was done within 60 minutes prior to patch application.

Subject Well Being Questionnaire was done before patch application and at 4, 10 and 24 hours post-patch application and at the ambulatory visit. All in house adverse event monitoring (subject well being questionnaire) was done with a window period of ± 30 minutes to the scheduled time except pre-patch application SWBQ which was done within 60 minutes prior to patch application.

Statistical methods:

Summary statistics, ANOVA, Ratio Analysis, 90% Confidence Interval, Intra subject variability and Power were calculated for Lidocaine 36 mg (1.8%). Geometric means and ratio of means were calculated for Lidocaine 36 mg (1.8%).

ANOVA was computed for Untransformed and Ln-transformed pharmacokinetic parameters of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Lidocaine 36 mg (1.8%).

A 90% confidence intervals for the ratio of the Treatment (A, B and C) products averages (geometric least square means) were calculated for Lidocaine 36 mg (1.8%) by first calculating the 90% Confidence Interval for the differences in the averages (least square means) of the log transformed data and then taking the anti-logs of the obtained confidence limits.

The comparison of interest is A vs C and B vs C, so the ratios were in the form of Treatment (A)/ Treatment (C) and Treatment (B)/ Treatment (C).

Ratio of means were calculated using the LSM for Ln transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Ratio of means were expressed as a percentage of the LSM for the test formulation.

Name of Sponsor / Company: Scilex Pharmaceuticals, Inc. **Name of Finished Product:** **Test Product** Lidocaine Patch 36 mg (1.8%). **Name of Active Ingredients:** Lidocaine.	Individual study table referring to part of the dossier Volume: 01	(for national authority use only)

Ratio (%) of Test formulations for each individual subjects were provided for untransformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, along with mean, standard deviation and co-efficient of variation for Lidocaine 36 mg (1.8%).

All statistical analyses for Lidocaine 36 mg (1.8%) were performed using PROC GLM of SAS® Release 9.4 (SAS Institute Inc., USA).

Adhesion Analysis :
Adhesion Analysis included all patches from 12 subjects and no patches fell off during the study, or were removed early for unacceptable irritation, or dropped out of the study before the end of the 12-hour application.

For each subject, the adhesion scores for each treatment (A, B, and C) at each time point were calculated as average of 3 patches (Patches 1, 2, and 3). *(Refer table 07 for Individual Adhesion scores at each assessment time point for all subjects.)*

The primary endpoint of adhesion was the Cumulative Adhesion Score (CAS) during the 12-hour application period (i.e. the CAS for a specific subject was the sum of the adhesion scores recorded immediately after the patch has been applied (0 hour) +0.5, +3, +6, +9, and +12 hours after application). Descriptive statistics (e.g. mean, standard deviation, median, minimum and maximum) on CAS was generated.

Mean CAS (i.e. score obtained by dividing the CAS with total number of observations) was provided. Descriptive statistics (e.g. mean, standard deviation, median, minimum and maximum) on mean CAS was generated.

In addition to mean scores, proportion of subjects with a meaningful degree of detachment (i.e. score ≥ 3) was provided.

(Refer table 08 for Individual Average Adhesion scores with Cumulative & Mean adhesion scores of all subjects.)

Name of Sponsor / Company: Scilex Pharmaceuticals, Inc.	Individual study table referring to part of the dossier	(for national authority use only)
Name of Finished Product: **Test Product** Lidocaine Patch 36 mg (1.8%).		
Name of Active Ingredients: Lidocaine.	Volume: 01	

Adhesion analysis for Lidocaine 36 mg (1.8%) was performed using SAS® Release 9.4 (SAS Institute Inc., USA).

Summary-Conclusions:

Efficacy results (Pharmacokinetics)

The mean pharmacokinetic parameters of Lidocaine 36 mg (1.8%) for Treatments (A, B and C) are summarized in the following tables.

Descriptive Statistics of Formulation Means for Lidocaine 36 mg (1.8%) (N= 12)

Parameter (Unit)	Mean ± SD (Un-transformed data)		
	Treatment (A)	Treatment (B)	Treatment (C)
C_{max} (ng/mL)	90.47750 ± 25.413083	160.27500 ± 100.061002	97.59333 ± 36.869199
$AUC_{0\rightarrow t}$ (hr. ng/mL)	1328.80587 ± 461.660141	1718.70939 ± 1004.00502	1487.39290 ± 590.006714
$AUC_{0\rightarrow\infty}$ (hr. ng/mL)	1344.07581 ± 458.186710	1731.27168 ± 1005.03640	1501.09829 ± 588.427583
$AUC_{\%Extrapolation}$	1.36226 ± 2.211383	0.89693 ± 1.112316	1.07191 ± 1.534819
T_{max} (hr)*	9.00 (9.00-18.00)	9.00 (9.00-16.05)	11.50 (9.00-14.00)
K_{el} (hr^{-1})	0.12803 ± 0.024237	0.13509 ± 0.029065	0.13874 ± 0.029814
$t_{½}$ (hr)	5.602 ± 1.1134	5.390 ± 1.3381	5.230 ± 1.2029

**For T_{max} Median has been represented instead of Mean and Range instead of SD.*

Geometric east Square Mean, Ratios, 90% Confidence interval, ISCV and Power for Lidocaine 36 mg (1.8%)

Parameter	Lntransformed Data			
	Geometric Mean			Intra Subject CV (%)
	Treatment-A	Treatment-B	Treatment-C	
C_{max}	87.26618	134.43924	91.72151	24.4
$AUC_{0\rightarrow t}$	1264.1557	1513.1016	1400.7028	17.9
$AUC_{0\rightarrow\infty}$	1281.9217	1526.8849	1416.0394	17.4

Name of Sponsor / Company: Scilex Pharmaceuticals, Inc. **Name of Finished Product:** **Test Product** Lidocaine Patch 36 mg (1.8%). **Name of Active Ingredients:** Lidocaine.	Individual study table referring to part of the dossier Volume: 01	(for national authority use only)

Parameter	Ln-transformed Data				
	(A/C) Ratio %	90% Confidence Intervals (A / C)	(B/C) Ratio %	90% Confidence Intervals (B / C)	Power (%)
C_{max}	95.14	80.30-112.73	146.57	123.71-173.66	70
$AUC_{0\rightarrow t}$	90.25	79.65-102.26	108.02	95.34-122.40	90
$AUC_{0\rightarrow \infty}$	90.53	80.15-102.25	107.83	95.46-121.79	92

Adhesion analysis:

The cumulative adhesion score and mean adhesion score of Lidocaine 36 mg (1.8%) are summarised in the following tables.

Descriptive Statistics of Cumulative and Mean adhesion scores of Lidocaine 36 mg (1.8%) (N= 12)

Statistics	Treatment*	N	Minimum	Maximum	Mean	S.D.	CV (%)
Cumulative Adhesion Score	A	12	0	5	2.00	2.335	116.8
	B	12	0	2	0.42	0.793	190.3
	C	12	0	0	0.00	0.000	Missing
Mean Adhesion Score	A	12	0	1	0.33	0.389	116.8
	B	12	0	0	0.07	0.132	190.3
	C	12	0	0	0.00	0.000	Missing

Subjects with meaningful degree of detachment (i.e. score ≥ 3):

Name of Sponsor / Company: Scilex Pharmaceuticals, Inc. **Name of Finished Product:** **Test Product** Lidocaine Patch 36 mg (1.8%). **Name of Active Ingredients:** Lidocaine.	Individual study table referring to part of the dossier Volume: 01	(for national authority use only)

Treatment*	No. of Subjects	Proportion of Subjects (%)
A	0	0
B	0	0
C	0	0

** Treatment- A: With Physical exercise B: With Heating & C: Under Normal conditions*

Safety results:

- All the subjects' vital signs were within normal range or considered not clinically significant by an investigator.
- All the subjects were in normal healthy status at the time of Subject Well Being Questionnaire.
- Over all six (06) adverse events were reported in four (04) subjects in entire duration of the study.
- Three (03) adverse events were reported in two (02) subjects in Period-I.
  - Subject (b) (6) had Headache (02 times) and were considered possibly related to the treatment (B).
  - Subject (b) (6) had Light headed secondary to exercise and was considered unrelated to the study drug .
- One (01) adverse event was reported in one (01) subject in Period-Iwash-out.
  - Subject (b) (6) had Menstrual Cramps and was considered unrelated to the study drug .
- One (01) adverse event was reported in one (01) subject in period-II.
  - Subject (b) (6) had Headache and was considered possibly related to the treatment (C).

Name of Sponsor / Company: Scilex Pharmaceuticals, Inc. **Name of Finished Product:** **Test Product** Lidocaine Patch 36 mg (1.8%). **Name of Active Ingredients:** Lidocaine.	Individual study table referring to part of the dossier Volume: 01	(for national authority use only)

- One (01) adverse event was reported in one (01) subject in period-III.
  - Subject (b) (6) had Head cold and was considered unrelated to the study drug .
- Serious/significant adverse events: No serious adverse events were reported during the entire duration of the study.
- No deaths were reported during the entire duration of the study.

Conclusion:

Efficacy conclusion:

Comparison of Treatment- A: with physical exercise Vs Treatment- C: under normal conditions:

The mean values of the primary PK parameters, C_{max}, $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow\infty}$, were lower during Treatment- A (with physical exercise) than during Treatment- C (under normal conditions), by 7%, 11% and 10% respectively. The 90% Confidence Intervals for the Treatment A vs. Treatment C ratios of ln-transformed PK parameter all fell within the range of 79.65 to 112.73, suggesting the effects of physical exercise on the rate and extent of Lidocaine 36 mg (1.8%) absorption was not significant. The median T_{max} was 9.0 h for Treatment- A (with physical exercise) and 11.5 h for Treatment- C (under normal conditions). The half-life observed was similar for Treatment A (5.602 h) and Treatment C (5.230 h).

Comparison of Treatment- B: with heating Vs Treatment- C: under normal conditions:

The mean values of the primary PK parameters, C_{max}, $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow\infty}$, were higher during Treatment- B (with heating) than during Treatment- C (under normal conditions) by 64%, 16% and 15% respectively. The 90% Confidence Interval for the Treatment A vs. Treatment B ratio of ln-transformed C_{max} (123.71 to 173.66) fell outside the 80-125% limits, suggesting that heating resulted in a significant increase in Lidocaine 36 mg (1.8%) absorption resulting in a higher C_{max} than under normal conditions. The corresponding ranges for $AUC_{0\rightarrow t}$

Name of Sponsor / Company: Scilex Pharmaceuticals, Inc. **Name of Finished Product:** **Test Product** Lidocaine Patch 36 mg (1.8%). **Name of Active Ingredients:** Lidocaine.	Individual study table referring to part of the dossier Volume: 01	(for national authority use only)

(95.34 to 122.40) and $AUC_{0\rightarrow\infty}$, (95.46 to 121.79) were within the 80-125% range, suggesting that the effect of heating on these parameters was not significant. As seen in Figure 1, the effects of heating were mainly evident at the 9-hour time point (immediately following 20 minutes of heating starting at 8.5 h), with little difference observed between the three treatments at other time points at which Lidocaine 36 mg (1.8%) concentrations were measured. Lidocaine 36 mg (1.8%) concentrations at 9 h were 171.8 ± 96.3 ng/mL after heating, compared to 88.5 ± 25.4 for Treatment A and 92.9 ± 39.7 ng/mL for Treatment C. Thus, the effects of heating on Lidocaine 36 mg (1.8%) absorption appeared to be immediate and reversible. Given the timing of heat application used in this study, heating increased the C_{max} via an immediate effect on the 9-hour time point, with little overall effect on the AUC. The median T_{max} was 9.0 h for Treatment- B (with heating) and 11.5 h for Treatment- C (under normal conditions). The half-life observed was similar for Treatment B (5.390 h) and Treatment C (5.230 h). The observed intra-subject coefficient variation (ISCV) for C_{max} was found to be 24.4%, indicating a higher variability in exposure during Treatment- B (with heating).

The overall coefficient variation obtained from descriptive statistics for Treatment- B (with heating) was found to be twice in comparison with that of Treatment- C (under normal conditions) and Treatment- A (with physical exercise).

Conclusion of adhesive performance:

Considering the adhesion scores of the subjects at all assessment time points and the proportion of subjects with a meaningful degree of detachment (i.e. score ≥3) in all the treatment conditions (A, B & C), it was concluded that only 50% of subjects had ≥90% adhesion (Score-0).

Adhesion analysis for Lidocaine 36 mg (1.8%) was performed using SAS® Release 9.4 (SAS Institute Inc., USA).

Name of Sponsor / Company: Scilex Pharmaceuticals, Inc.	Individual study table referring to part of the dossier	(for national authority use only)
Name of Finished Product: **Test Product** Lidocaine Patch 36 mg (1.8%).		
Name of Active Ingredients: Lidocaine.	Volume: 01	

Safety Conclusion:

- The study was conducted as per the protocol bearing Study No.A15.0188, Version No: 01 dated 05JAN16 which was approved by (b) (4) Institutional Review Board on 06JAN16.
- Study started with twelve (12) subjects and all subjects completed the study.
- No SAEs were reported.
- Over all six (06) adverse events were reported in four (04) subjects in entire duration of the study. Three (03) adverse events were considered possibly related to the study drug and remaining three (03) were considered unrelated.
- **Serious/significant adverse events**: No serious adverse events were reported during the entire duration of the study.
- **Deaths:** No deaths were reported during the entire duration of the study.

Overall, Lidocaine Patch 36 mg/patch (1.8%) was well tolerated as a single, application patch (3 x [36 mg/patch, 1.8 %]) when applied healthy, adult, human subjects.

Date of the report: 22DEC16

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

/s/

WEI QIU
01/29/2018

YUN XU
01/30/2018

CLINICAL PHARMACOLOGY REVIEW

NDA: 207962	Submission Date: July 10, 2015; November 19, 2015; January 11, 2016; March 18, 2016
Proposed Brand Name	ZTlido
Generic Name	Lidocaine patch 1.8%
Reviewer	Wei Qiu, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	DCPII
OND division	DAAAP
Sponsor	Scilex Pharmaceuticals, Inc.
Relevant IND(s)	IND 111537
Submission Type	Original Submission; 505(b)(2)
Formulation; Strength(s)	Topical patch; 1.8%
Dosage and Administration	Up to 3 patches for up to 12 hours in a 24-hour period (12 hours on and 12 hours off)
Indication	Relief of pain associated with post-herpetic neuralgia

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the NDA submissions dated July 10, 2015, November 19, 2015, January 11, 2016, and March 18, 2016. Based on the discussion at the PIND stage, the Division agreed that if the Sponsor can demonstrate equivalent systemic exposure between the proposed product (lidocaine patch 1.8%) and the listed drug, Lidoderm (lidocaine) patch 5%, then no additional clinical efficacy study will be required. This comparative bioavailability study will be the pivotal study for approval of this NDA. Sponsor conducted the comparative bioavailability study (SCI-LIDO-PK-001) and intended to demonstrate that three patches of lidocaine patch 1.8% will provide comparable lidocaine systemic exposure as three patches of Lidoderm patch 5%. Although the approved labeling for Lidoderm patch 5% does not recommend the use of tape or overlay, surgical tape was used on both the proposed lidocaine patch 1.8% and the listed drug, Lidoderm patch 5%, in all subjects in Study SCI-LIDO-PK-001. Sponsor did not provide sufficient evidence to justify that the use of tape will not affect lidocaine absorption from Lidoderm patch 5%. Therefore, the PK bridging to the Agency's previous findings on efficacy and safety for Lidoderm patch 5% is not adequately established. To resolve the deficiency in establishing a sufficient PK bridging, the list drug product, Lidoderm patch 5%, must be used according to the approved package insert (e.g., without use of an overlay or tape) in a comparative bioavailability study with the proposed drug product and list drug product.

In addition, the sponsor evaluated the effect of heat and exercise in Study SCI-LIDO-PK-001. The effects of heat and exercise on lidocaine absorption from lidocaine patch 1.8% were assessed by applying patches after heat treatment or exercise instead of applying a heating pad directly on the patches or exercising while wearing the patches. Therefore, the study results do not reflect the effect of exercise and the effect of heat, and are not acceptable. The evaluation of heat and exercise is generally not considered pivotal because the external factors such as heat and exercise can be handled by labeling. If sponsor chooses to evaluate the effects of external factors such as heat, exercise and overlay on the systemic absorption of lidocaine from the proposed product, then they

need to design the studies so that study subjects are wearing the patch while doing exercise, applying a heat pad or using an overlay.

Sponsor indicated in the submission dated March 18, 2016 that a late submission including a new study for the evaluation of heat and exercise effect (Study SCI-LIDO-HEX-001) will be submitted within 2 months of the PDUFA due date. These data will not be reviewed in this review cycle based on review team discussion.

The number of subjects (n = 4) in geriatric population (≥ 65 years of age) is relatively small to characterize the PK adequately for this population. Limited data in the geriatric population did not showed much difference in systemic exposure in comparison to subjects < 65 years of age for lidocaine patch 1.8% or Lidoderm patch 5%. Due to the small sample size of the geriatric population, no definitive conclusion can be made.

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the clinical and analytical portions of comparative bioavailability study SCI-LIDO-PK-001 and recommended that the PK data from Study SCI-LIDO-PK-001 should be accepted for further agency review but the residual drug in used patches should not be accepted (see Dr. Srinivas Rao N Chennamaneni's review dated March 24, 2016).

An Inter-Divisional OCP Briefing was held on April 5, 2016. There were some discussions on whether or not tape should be allowed to use on the reference product, Lidocaine patch 1.8% is very different from Lidoderm patch 5% in terms of drug concentration (1.8% vs 5% in Lidoderm), drug load (36 mg vs 700 mg in Lidoderm) and formulations. Therefore, establishing equivalent systemic exposures between lidocaine patch 1.8% and Lidoderm patch 5% with the use of tape cannot warrant equivalent systemic exposure under labeled conditions (e.g., without the use of tape). Without knowing the effect of taping on Lidoderm patch 5%, adequate PK bridging to Lidoderm is not established.

Phase IV Commitments
None.

1.2 Summary of Clinical Pharmacology Findings

Lidocaine is an amide-type local anesthetic agent and is suggested to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses. Lidoderm Patch 5% is the approved NDA (NDA 20-612) lidocaine patch product for topical treatment of pain associated with post-herpetic neuralgia (PHN). Maximum of 3 patches can be applied only once for up to 12 hours within a 24 hour period.

Sponsor developed Lidocaine patch 1.8% to be equivalent to Lidoderm patch 5% and intended to improve drug delivery and adhesion properties. The proposed lidocaine patch 1.8% has the same surface area as Lidoderm patch 5%, which is 10 x 14 cm^2. Sponsor stated that the improvement in drug delivery allows for the each lidocaine patch 1.8% product to be compounded with 36 mg of lidocaine, versus 700 mg lidocaine within each Lidoderm Patch 5%.

Sponsor submitted a 505(b)(2) NDA 207-962 for lidocaine patch 1.8% and proposed to rely on the Agency's previous finding of the safety and efficacy of the listed drug, Lidoderm Patch 5% (NDA 20-612) via the establishment of a PK bridge. Based on discussion in the PIND stage, the Division agreed that if the Sponsor can demonstrate equivalent systemic exposure between the proposed product and the listed drug, Lidoderm, then no additional clinical efficacy study will be required.

The clinical/clinical pharmacology database for this NDA consists of one comparative bioavailability study (Study SCI-LIDO-PK-001) conducted in healthy volunteers and three dermal safety studies (SCI-LIDO-PHOTO-001, SCI-LIDO-PHOTO-002, and SCI-LIDO-DERM-001). Comparative bioavailability study (SCI-LIDO-PK-001 Cohort 1) was conducted in order to demonstrate that three patches of lidocaine patch 1.8% would provide comparable lidocaine systemic exposure as three patches of Lidoderm patch 5%. For Lidoderm, the Agency's previous findings on safety and effectiveness were established under the label recommended instruction. Although the approved labeling for Lidoderm patch 5% does not recommend the use of tape or overlay, surgical tapes were used on both the proposed lidocaine patch 1.8% and the listed drug, Lidoderm patch 5%, in all subjects in Study SCI-LIDO-PK-001. Sponsor did not provide sufficient

evidence to justify that the use of tape would not affect lidocaine absorption from Lidoderm patch 5%. The proposed lidocaine patch 1.8% and the listed drug, Lidoderm patch 5% differ significantly in terms of formulations. Therefore, the effect of tape on lidocaine absorption can be significantly different between the 1.8% patch and Lidoderm patch 5%; establishing equivalent systemic exposure between the two products with the use of tape cannot warrant equivalent systemic exposure without the use of tape. Therefore, the PK bridging between the proposed lidocaine patch 1.8% and Lidoderm patch 5% has not been sufficiently established. In Study SCI-LIDO-PK-001 Cohort 2, the effects of heat and exercise on lidocaine absorption from lidocaine patch 1.8% were assessed by applying patches after heat treatment or exercise instead of applying a heating pad directly on the patches or exercising while wearing the patches. Therefore, the study results do not reflect the effect of exercise and the effect of heat and this part of the study is not reviewed.

(b) (4)

(b) (4)

Table 1 Summary of Equivalence Analyses for the Lidocaine PK of Three Patches of Lidocaine Patch 1.8% and Three Patches of Lidoderm Patch 5% in the General (N = 52) and All Populations (N = 56)

(b) (4)

2 Question Based Review

2.1 General Attributes of the Drug

1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug product?

Lidoderm® Patch 5% (NDA 20-612) is the approved NDA product for the treatment of pain associated with PHN. According to Lidoderm® labeling, a maximum of 3 patches may be applied only once for up to 12 hours within a 24 hour period.

Sponsor developed Lidocaine patch 1.8% to be equivalent to Lidoderm patch 5% and intended to improve drug delivery and adhesion properties. The proposed lidocaine patch 1.8% has the same size as Lidoderm, which is 10 x 14 cm^2. Sponsor stated that the improvement in drug delivery allows for the lidocaine patch 1.8% product to be compounded with 36 mg of lidocaine, versus 700 mg lidocaine within the Lidoderm patch 5%.

Sponsor submitted a 505(b)(2) NDA 207962 for lidocaine patch 1.8% and proposed to rely on the Agency's previous finding of the safety and efficacy of the listed drug, Lidoderm (NDA 20612). Based on discussion in the PIND stage, the Division agreed that if the Sponsor can demonstrate equivalent systemic exposure between the proposed

product and the listed drug, Lidoderm, then no additional clinical efficacy study will be required. To establish a PK bridge with the listed drug, Lidoderm patch 5%, sponsor conducted one pivotal comparative bioavailability study (Study SCI-LIDO-PK-001) in healthy volunteers.

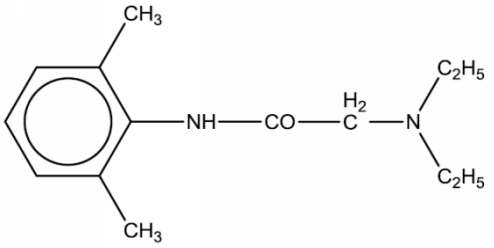
2. What are the communications during product development?

At the early stage of this product development (Pre-IND meeting minutes dated May 10, 2011), sponsor was recommended to collect PK data from individuals who have the patch adhered to the applied area of skin without any detachment in the proposed comparative bioavailability study. In addition, it was advised that the use of reinforcement at any time for adhesion to skin (e.g., tape or overlay) is unacceptable. At the Pre-NDA meeting (Meeting minutes dated March 20, 2015), sponsor stated that all subjects had their patches (both lidocaine patch 1.8% and Lidoderm patch 5%) reinforced with tape. The Division expressed the concern that the use of tape may have an effect on the results of the study and advised sponsor to provide adequate data to demonstrate that using reinforcement to Lidoderm patch 5% did not affect the systemic exposure of lidocaine. In the NDA submission, to justify that the use of tape will not affect lidocaine absorption, sponsor stated that "breathability" of the 3M micropore surgical tape (Transpore) used in the pivotal comparative bioavailability study and the small surface area of coverage combined is not expected to alter the PK of lidocaine. No other data were provided to justify that the use of tape would not affect lidocaine absorption. Thus, Sponsor's justification is not adequate to exclude the impact of the use of tape on lidocaine absorption from either Lidoderm patch 5% or lidocaine patch 1.8%.

3. What are the highlights of the chemistry and physico-chemical properties of the drug substances, and the formulation of the drug product?

Table 2 Physical-Chemical Properties of Lidocaine

Drug Name	Lidocaine
Chemical Name	Acetamide, 2-(diethylamino)-N-(2,6-dimethylpheny)-

Structure	 $C_{14}H_{22}N_2O$
Molecular Weight	234.34
Appearance	White or almost white crystalline powder
Solubility	Insoluble in water, very soluble in alcohol, benzene, and ethyl ether, soluble in chloroform and oils

ZTlido is a single-layer, drug-in-adhesive patch. Each patch contains 36 mg of lidocaine. The components and compositions of lidocaine patch 1.8% formation are listed in **Table 3**. The proposed lidocaine patch 1.8% has the same dimensions and surface areas (10 x 14 cm^2) as the listed product, Lidoderm (lidocaine patch 5%).

Table 3 Components and Composition of Lidocaine Patch 1.8%

Component	Quality Standard	Function	Composition	
			mg/patch	% Composition
Lidocaine	USP	Active	36	1.80
Butylated hydroxytoluene	NF	(b) (4)		(b) (4)
Silicon dioxide	NF			
Dipropylene glycol	JPE			
Isostearic acid	JPE			
Mineral oil	USP			
Polyisobutylene (low molecular weight)	NF			
Polyisobutylene (high molecular weight)	NF			
Styrene/isoprene/styrene block copolymer	JPE			
Terpene resin	JPE			
Polyethylene terephthalate separator	JPE	Release liner	140 cm^2/patch	
Nonwoven cloth	JP	Backing (b) (4)	140 cm^2/patch	

NF: National Formulary
USP: Unites States Pharmacopeia

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

Lidocaine is an amide-type local anesthetic. Lidocaine blocks sodium ion channels required for the initiation and conduction of neuronal impulses which, in certain instances, results in local anesthesia. When applied to intact skin, ZTlido provides local dermal analgesia by the release of lidocaine from the patch into the skin. The penetration of lidocaine into intact skin after application of ZTlido is sufficient to produce an analgesic effect, but less than the amount necessary to produce a complete sensory block.

The proposed indication is for relief of pain associated with post-herpetic neuralgia.

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

ZTlido is a single-layer, drug-in-adhesive patch delivery system in which the drug is (b) (4) in the adhesive layer.

ZTlido is for topical administration only.

2.2 General Clinical Pharmacology

1. What is known about the PK characteristics of lidocaine for the listed drug, Lidoderm?

Absorption: The amount of lidocaine systemically absorbed from LIDODERM is directly related to both the duration of application and the surface area over which it is applied. In a PK study conducted in 15 normal volunteers, three LIDODERM patches were applied over an area of 420 cm^2 of intact skin on the back of normal volunteers for 12 hour. Blood samples were withdrawn for determination of lidocaine concentration during the application and for 12 hours after removal of patches. The mean (± SD) Cmax of lidocaine is 0.13 (± 0.06) µg/mL (about 1/10 of the therapeutic concentration required to treat cardiac arrhythmias). Median Tmax value is 11 hour. The mean (± SD) amount of lidocaine absorbed into the systemic circulation is 64 (± 32) mg. The total amount of lidocaine in 3 patches of LIDODERM patches is 2100 mg. When LIDODERM is used

according to the recommended dosing instructions, only 3 ± 2% of the dose applied is expected to be absorbed. Repeated application of three patches simultaneously for 12 hours (recommended maximum daily dose), once per day for three days, indicated that the lidocaine concentration does not increase with daily use.

Distribution: When lidocaine is administered intravenously to healthy volunteers, the volume of distribution is 0.7 to 2.7 L/kg (mean 1.5 ± 0.6 SD, n = 15). At concentrations produced by application of LIDODERM, lidocaine is approximately 70% bound to plasma proteins, primarily alpha-1-acid glycoprotein. At much higher plasma concentrations (1 to 4 µg/mL of free base), the plasma protein binding of lidocaine is concentration dependent. Lidocaine crosses the placental and blood brain barriers, presumably by passive diffusion.

Metabolism: It is not known if lidocaine is metabolized in the skin. Lidocaine is metabolized rapidly by the liver to a number of metabolites, including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacologic activity similar to, but less potent than that of lidocaine. A minor metabolite, 2,6-xylidine, has unknown pharmacologic activity but is carcinogenic in rats. The blood concentration of this metabolite is negligible following application of LIDODERM (lidocaine patch 5%). Following intravenous administration, MEGX and GX concentrations in serum range from 11 to 36% and from 5 to 11% of lidocaine concentrations, respectively.

Excretion: Lidocaine and its metabolites are excreted by the kidneys. Less than 10% of lidocaine is excreted unchanged. The half-life of lidocaine elimination from the plasma following IV administration is 81 to 149 minutes (mean 107 ± 22 SD, n = 15). The systemic clearance is 0.33 to 0.90 L/min (mean 0.64 ± 0.18 SD, n = 15).

2. What moieties in the plasma are appropriately identified and measured to assess the pharmacokinetics?

Lidocaine is measured in the PK study SCI-LIDO-PK-001.

2.3 Intrinsic Factors

1. What is the pediatric plan?

Sponsor is not requesting a waiver for pediatric studies because they believe that this NDA submission does not trigger the Pediatric Research Equity Act as the drug product does not involve a new chemical entity, a new indication, new dosage form, or a new route of administration. An initial Pediatric Study Plan (iPSP) was submitted to IND 111537 on July, 15, 2014 for this drug product. An FDA iPSP response letter (dated September 19, 2014) advised that a PSP is not required as PREA will not likely to be applied to this drug product.

2.4 General Biopharmaceutics

1. What are the relative bioavailabilities of lidocaine following the application of lidocaine patch 1.8% in comparison to Lidoderm patch 5%?

(b) (4)

In Study SCI-LIDO-PK-001 Cohort 1, the relative bioavailability of lidocaine was performed as a single dose, two-way cross-over design with the application of three patches of either the lidocaine patch 1.8% or the listed drug product, Lidoderm patch 5%. There is a washout period of 7 days between treatments. Each patch was applied to a defined area of normal skin on the back of each volunteer for 12 hours. All patches were reinforced with 3M paper tape on the corners and monitored for completeness of adhesion. If any lifting of the patches was observed during the dosing period, the edge of the lifting area would be reinforced with additional paper tape.

Blood samples for PK were collected from each subject at pre-dose, and then at 2, 4, 6, 9, 10, 11, 12, 13, 14, 16, 18, 20, 22, 24, and 48 hours post-dose patch application.

(b) (4)

Table 4 Summary of Lidocaine PK parameters in Healthy Subjects Following a Single-Dose Application of Three Patches of Lidocaine Patch 1.8% and Three Patches of Lidoderm Patch 5% for 12-Hour Duration (Study SCI-LIDO-PK-001 Cohort 1)

(b) (4)

(b) (4)

However, the two products are not considered PK bridged because the approved labeling for Lidoderm patch 5% did not recommend the use of any reinforcement on the patch and sponsor did not provide sufficient evidence to justify that the use of tape will not affect lidocaine absorption.

2. What is the absolute dose of lidocaine absorbed from three lidocaine patch 1.8%?

(b) (4)

In Study SCI-LIDO-PK-001 Cohort 1, all subjects received an IV bolus dose of 0.7 mg/kg infused at a rate of 25 mg/min on Day 1. After a 7-day washout period, subjects were randomized to receive either three patches of lidocaine patch 1.8% or three patches of Lidoderm patch 5% on Day 8 depending on the study sequence. After a 7-day washout period, the application was crossed over to the other treatment on Day 15 for each subject. All patches were reinforced with 3M paper tape on the corners and monitored for completeness of adhesion. If any lifting of the patches was observed during the dosing period, the edge of the lifting area was reinforced with additional paper tape. Lidocaine PK parameters are summarized in **Table 5**.

Table 5 Summary of Lidocaine PK Parameters for Lidocaine IV Bolus Dose (0.7 mg/kg), Three Patches of Lidocaine Patch 1.8%, and Three Patches of Lidoderm Patch 5% (Study SCI-LIDO-PK-001 Cohort 1)

(b) (4)

2.5 Analytical Section

1. *Do the bioanalytical methods adequately validated for determining plasma concentrations of lidocaine?*

Validated LC/MS/MS method was used for the determination of lidocaine in human plasma. The assay precision and accuracy of the analytical methods are summarized in **Table 6**.

Table 6 Lidocaine Assay Precision and Accuracy

	Study SCI-LIDO-PK-001
Nominal range for the calibration curve	0.500 – 300 ng/mL
LLOQ	0.500 ng/mL
QC	1.50, 15, 150, and 225 ng/mL
Precision (%CV)	3.57 – 4.8%
Accuracy (% difference from theoretical)	-4.17 – 5.96%

3 Labeling Recommendations

Labeling review was not conducted because this proposed product is not going to be approved at this review cycle.

4 Appendix

4.1 Clinical Pharmacology Filing Memo

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	207-962	Proposed Brand Name	ZTlido Patch
OCP Division (I, II, III, IV, V)	II	Generic Name	Lidocaine patch 1.8%
Medical Division	DAAAP	Drug Class	Amide-type local anesthetic agent
OCP Reviewer	Wei Qiu, Ph.D.	Indication(s)	Relief of pain associated with post-herpetic neuralgia
OCP Team Leader	Yun Xu, Ph.D.	Dosage Form, Strength	Topical patch, 1.8%
Pharmacometrics Reviewer	N/A	Dosing Regimen	Up to 3 patches for up to 12 hours in a 24-hour period (12 hours on and 12 hours off)
Date of Submission	July 10, 2015	Route of Administration	topical
Primary Review Goal Date (GRMP)	April 7, 2016	Sponsor	Scilex Pharmaceuticals, Inc
		Priority Classification	Standard
PDUFA Due Date	May 10, 2016	Relevant INDs	IND 111537

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	1		Study SCI-LIDO-PK-001
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 1:				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				

Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability	x	(1)		
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	(1)		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			√	Sponsor stated that the to-be-marketed formulation is the same that was used in Study SCI-LIDO-PK-001
2	Has the applicant provided metabolism and drug-drug interaction information?			√	No new findings in the proposed label.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	√			Relative BA study was conducted with the list drug Lidoderm 5% patch
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	√			
5	Has a rationale for dose selection been submitted?			√	Match the exposure of the list drug
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	√			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	√			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	√			

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	√			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			√	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	√			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			√	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			√	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			√	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			√	Submitted pediatric plan
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			√	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	√			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	√			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			√	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES

This NDA is fileable from clinical pharmacology perspective. OSI inspection was requested for the relative BA study on August 27, 2015. The requested action goal date is March 24, 2016.

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. **In your comparative BA study SCI-LIDO-PK-001, you stated that you have used surgical type on your proposed product and the list drug, Lidoderm, in all subjects. This topic was raised in the pre-NDA meeting and you were asked to provide justification that using tapes will not affect the PK of Lidoderm. Although in the NDA submission you provided estimation on the area covered by tape and stated that the coverage of tape is not expected to alter the PK, no other convincing data are provided to justify that the use of tape will not affect lidocaine absorption from either your proposed product or Lidoderm patch. Whether this justification is adequate or not will be a review issue. If the justification is not acceptable, you will need to either conduct another comparative BA study using your proposed product and Lidoderm (the use of Lidoderm need be based on the approved Package Insert), or provide additional data to demonstrate that adding the tape did not affect the systemic exposure of lidocaine.**
2. **In Study SCI-LIDO-PK-001 Cohort 2, your proposed lidocaine patches were applied after heat treatment or exercise instead of applying a heating pad directly on the patches or exercising while wearing the patches.** (b) (4)

(b) (4)

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

Background:

Scilex Pharmaceuticals Inc submitted a 505(b)(2) NDA 207-962 for ZTlido Patch (lidocaine patch 1.8%). The proposed indication is for the relief of pain associated with post-herpetic neuralgia.

This NDA relies on the Agency's previous findings of safety and effectiveness for Lidoderm Patch, 5% (NDA 20612). Sponsor stated that the to-be-marketed formulation is the same as that was used in the relative BA study SCI-LIDO-PK-001.

The clinical pharmacology/clinical program includes one relative BA study SCI-LIDO-PK-001 and three dermal safety studies (SCI-LIDO-PHOTO-001, SCI-LIDO-PHOTO-002, and SCI-LIDO-DERM-001 (adhesion was evaluated)). Relative BA study SCI-LIDO-PK-001 consists of two cohorts. In Cohort 1, 52 young and 4 geriatric healthy volunteers received lidocaine IV 0.7 mg/kg single bolus dose, 3 lidocaine patch 1.8% and 3 Lidoderm patch 5% with patches remaining in place for 12 hours. In Cohort 2, after heat treatment or exercise regimen, 3

lidocaine patches 1.8% were applied 5 min later and remained in place for 12 hours. Surgical tape was applied to the corners of each test patch or reference patch (total of 9 cm2) initially and additional tape was used to reinforce loose edges if lack of adhesion was noted during the 12-hour dosing period. Sponsor concluded that (b) (4) (b) (4) no heat or exercise effect was found.

Please find the filing slides for more details.

BEST AVAILABLE COPY

NDA 207962:
ZTlido Patch (Lidocaine patch 1.8%)

- **Sponsor**: Scilex Pharmaceuticals Inc.
- Dosage form: Topical patch
- 505(b)(2) NDA
- Indication: for relief of pain associated with post-herpetic neuralgia (PHN)
- Listed Drug:
  - Lidoderm® Patch, 5%

1

Pre-IND MM (5/10/11)

(b) (4)

2

Pre-IND MM (5/10/11)

(b) (4)

Follow-up on BE Study Design (2/24/12)

(b) (4)

Follow-up on BE Study Design (2/24/12)

(b) (4)

Question 3. If bioequivalence between the two patches is established by the appropriate study, can labeling claim to lack of increase in plasma concentration with repeated use be made, as appears in the Lidoderm labeling: "……lidocaine concentration does not increase with daily use."

FDA Response

The information included in the label will be reviewed after the NDA is submitted. If bioequivalence is established, your product labeling may be similar to the reference drug.

In order to support safe use of your product, evaluate the effect of heat, exercise and overlay on the systemic bioavailability of the proposed patch formulation.

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Agency Response to Geriatric Recruitment Request (9/18/14)

Does the Division agree that 4 geriatric subjects (i.e., at ages greater than 65 years) is sufficient to assess geriatric pharmacokinetics contingent on the outcome of the study findings?

Agency Response:

We do not agree that four subjects is a sufficient number to assess geriatric pharmacokinetics (PK). Given that post-herpetic neuralgia occurs fairly often in this population, it is important to gather sufficient PK data in this population to support the further development of your drug product. We acknowledge your difficulties in recruiting at least 12 geriatric subjects given the protocol's inclusion and exclusion criteria. We are willing to accept some flexibility in the inclusion/exclusion criteria for this subset of individuals provided there is no compromise in subject safety. For example, you may decide to enroll subjects who are taking carefully selected prescription or over-the-counter medications but exclude subjects with significant cardiovascular history.

6

Pre-NDA MM (3/20/15)

Question 2: *Based upon the clinical studies conducted to demonstrate bioequivalence, as stated above, does FDA agree that Scilex has demonstrated bioequivalence to the reference product? Does FDA agree that the clinical data package is sufficient to conduct a review, and will not result in a Refusal-to-File (RTF)?*

FDA Response

The data supporting your claim of bioequivalence (BE) will be evaluated during the review process. If your product is demonstrated to be BE to Lidoderm, your proposed plan seems acceptable.

We acknowledge your justification for having applied the overlay for both the treatments in the completed BE study SCI-LIDO-PK-001. Although you maintain that your product has improved adhesion, we are unable to confirm this because your submission does not present comparative adhesion data at 12 hours, the labeled duration of application for the lidocaine patch. Because the lidocaine patch is approved for use without the use of an overlay, your application must bridge to the lidocaine patch used without an overlay. As Lidoderm was used with an overlay in the BE study, you must either repeat the study without the overlay, or provide adequate data to demonstrate that adding the overlay to Lidoderm did not affect its systemic exposure. If you can demonstrate that the overlay did not alter the pharmacokinetic profile of Lidoderm, and if you have demonstrated bioequivalence only with an overlay on your product, then your product will be labeled for use with an overlay. Include all data, including the geriatric data, in the BE analysis.

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Pre-NDA MM (3/20/15)

Discussion:

The Sponsor stated that they miscommunicated to the Division about use of an overlay in the bioequivalence study SCI-LIDO-PK-001. They clarified that, because the study protocol did not allow for an overlay, they incorporated only reinforcement around the edges of the patches with paper tape. They also stated that by using reinforcement, they were not able to assess adhesion in the study; instead, they performed a separate comparative adhesion assessment study. The Division stated that, because the lidocaine patch is approved for use without the use of an overlay, and the reinforcement tape might change results, the Sponsor will need to provide information about how much of the patch was covered with tape. This is (b) (4) The Division asked how many of the subjects had tape used and the Sponsor responded that all the subjects had their patches reinforced with tape to keep the corners from being dislodged. The Division informed the Sponsor that if the Sponsor's patch needs to be reinforced to be kept in place, then labeling will need to reflect that the product has to be used with tape. The Sponsor stated that they used a porous tape and inquired if the type of tape used might have an impact on the Division's view of the study. The Division responded that the type of tape used may have an effect on the results of the study.

The Division also informed the Sponsor that they will need to submit all datasets from the bioequivalence study in SAS-transport file format with a define pdf file explaining the dataset variables and overall format of the dataset.

8

Pre-NDA MM (3/20/15)

Question 3: *Does FDA agree that the pharmacokinetic data package is sufficient to conduct a review, and submission of the pharmacokinetic data package will not result in an RTF?*

FDA Response

Although we would have preferred PK data from at least 16 subjects, this is not a reason for a refusal to file. The adequacy of the data will be assessed during the NDA review.

Discussion:
The Sponsor accepted the FDA's response. No discussion occurred.

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Clin Pharm/Clin Program

- 1 Relative BA study SCI-LIDO-PK-001
  - PK of lidocaine patch 1.8% vs Lidoderm patch 5%
  - Effect of heat and exercise on PK of lidocaine patch 1.8%
- 3 dermal safety studies
  - SCI-LIDO-PHOTO-001
  - SCI-LIDO-PHOTO-002
  - SCI-LIDO-DERM-001

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Relative BA Study SCI-LIDO-PK-001

- R, SD, relative BA and effect of heat and exercise
- Treatment:
  - Cohort 1: 52 young (20 male/32 female) with mean age of 36.8 (range: 20-55 yrs) and 4 geriatric healthy volunteers (2 male/2 female) with mean age of 68.5 (range 66-75yrs)
    - Lidocaine IV 0.7 mg/kg single bolus dose
    - Three Lidocaine patch 1.8% (Arm 1) or three lidoderm 5% (Arm 2) on back, remained in place for 12 hours
  - Cohort 2:
    - After heat treatment, three lidocaine patches 1.8% applied and remained in place for 12 hours
    - After exercise regimen (walking at a moderate pace on a treadmill for ~ 20 min), three lidocaine patches 1.8% applied 5 min later
    - Without heat or exercise, three lidocaine patches applied and remained in place for 12 hours
- PK sampling: up to 48 h post dose

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Patch Application

The patch application and adhesion methods are described below. Both patches have the same dimensions of 10 cm x 14 cm (140 cm^2).

Lidoderm® Patch 5%:

- 3 patches were applied with the subject in a sitting position:

  Patch 1-to the right upper to mid back
  Patch 2-the left upper to mid back
  Patch 3-to the right mid back approximately 2 cm below Patch 1
- Transparent Liner was removed immediately prior to patch application
- Surgical tape was applied to the corners of each patch (approximately 2.25 cm^2 of each patch corner was covered with tape; total of 9 cm^2, which constitutes 6.4% of the patch surface area being reinforced with tape)
- If lack of adhesion was noted during the 12-hour dosing period, additional tape was used to reinforce loose edges for all 3 patches (assuming all 4 edges were reinforced, up to 31.4% of the patch surface area, is being reinforced with tape)
- Adhesion to the skin was checked at every blood sampling point
- Subjects were prohibited from pressing the back of the patch and were instructed to lay supine on the back within the 12-hour dosing period if they desired to lay down

Patch Application

Lidocaine Patch 1.8 %:

- 3 patches were applied in with the subject a sitting position:

  Patch 1-to the right upper to mid back
  Patch 2-the left upper to mid back
  Patch 3-to the right mid back approximately 2 cm below Patch 1

- Transparent Liner was removed prior to patch application by folding the center of the patch. When the liner popped out, the patch was placed on the back and folded into one side. Firstly one side of the liner was removed and half of the patch was applied to the skin and then the second part of the liner was removed allowing the second half of the patch to be applied to the skin

- Surgical tape was applied to the corners of each patch (approximately 2.25 cm^2 of the patch corner was covered with tape; total of 9 cm^2, which constitutes 6.4% of the patch surface area being reinforced with tape)

- If lack of adhesion was noted during the 12-hour dosing period, additional tape was used to reinforce loose edges for all 3 patches (assuming all 4 edges were reinforced, up to 31.4% of the patch surface area is being reinforced with tape)

- Adherence condition to the skin was at a minimum checked at every blood sampling point

- Subjects were prohibited from pressing the back of the patch and were instructed to lay supine on the back within the 12-hour dosing period if they desired to lay down

3

(b) (4)

Recommendation

- Sponsor stated that a 1.8% lidocaine patch with the commercial adhesive formulation was selected and demonstrated BE to Lidoderm® patch 5%
- Datasets of PK raw data and parameters are included
- Bioanalytical reports are included
- Filable from clin pharm perspective
- OSI inspection for the pivotal BA study was requested on August 27, 2015. Requested action goal date is March 24, 2016.

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4.2 Individual Study Summary

4.2.1 Study SCI-LIDO-PK-001

SYNOPSIS

SPONSOR: Scilex Pharmaceuticals, Inc. 101 Lindenwood Drive, Suite 225 Malvern, PA 19355	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER**	*(For National Authority Use Only)*
NAME OF FINISHED PRODUCT: Lidocaine Patch 1.8%	**VOLUME:**	
NAME OF ACTIVE INGREDIENT: Lidocaine	**PAGE:**	

STUDY TITLE:

Phase 1, Randomized, Comparative Pharmacokinetic Study of Bolus Intravenous Lidocaine 0.7 mg/kg, Lidocaine Patch 1.8%, and Lidocaine Patch 5% (Lidoderm®) in Healthy Subjects and an Evaluation on the Effects of Heat and Exercise on the Pharmacokinetics of Lidocaine Patch 1.8% in Healthy Subjects

INVESTIGATOR(S):

Phillip LaStella, MD

STUDY CENTER(S):

TKL Research, Inc.
One Promenade Blvd
Fair Lawn, NJ 07410

PUBLICATION REFERENCE: Not applicable.

STUDY PERIOD:

28 April 2014 – 24 July 2014

STUDY PHASE: 1

OBJECTIVES:

The primary objectives of the study were:

- To characterize the comparative single-dose pharmacokinetics (bioequivalence) of lidocaine patch 1.8% (investigational product) versus Lidoderm® (lidocaine patch 5%, reference product); and
- To characterize the single-dose pharmacokinetics of lidocaine 0.7 mg/kg bolus intravenous (IV) administered at 25 mg/min to support the determination of the apparent

dose and absolute bioavailability for each patch (test/reference) based on the generated pharmacokinetic parameter values of IV lidocaine, under fasting conditions.

The secondary objectives of the study were:

- To evaluate the comparative safety of a single dose of the investigational product and the two comparator treatments.
- To characterize the effects of applied heat and moderate exercise on the single-dose pharmacokinetics of a lidocaine patch 1.8% relative to the same lidocaine patch 1.8% applied under normal conditions.

METHODOLOGY:

Cohort 1, Part 1 – Lidocaine IV 0.7 mg/kg Single Bolus Dose: Eligible subjects were admitted to the study site on Day -1. On the morning of Day 1, subjects received a single bolus dose of lidocaine IV 0.7 mg/kg at a rate of 25 mg/minute. Subjects had continuous cardiac monitoring during the IV bolus administration that was continued up to 4 hours after the IV lidocaine bolus administration. Additionally, during the IV administration of lidocaine, it was required that a clinician be present who was well versed in diagnosis and management of cardiac arrhythmias and that oxygen and other resuscitative drugs were readily available.

Samples to determine blood levels of lidocaine were collected before the administration of bolus lidocaine IV 0.7 mg/kg (pre-dose) and at scheduled time points up to 24 hours after administration of the single bolus dose of lidocaine IV. Subjects completed a 7-day wash-out period after the bolus lidocaine IV administration on Day 1. Subjects were confined to the clinic up to Day 2 and then returned to the clinic in the evening of Day 7 (+ 3 days).

Cohort 1, Part 2 – Lidocaine Patch 1.8% (Arm 1) or Lidoderm® 5% (Arm 2): On Day 8, a set of 3 patches of either lidocaine 1.8% (Arm 1) or Lidoderm® 5% (Arm 2), depending on the randomization assignment, was applied to a defined area of normal skin on the subjects' backs. The patches remained in place for 12 hours.

If necessary, the patches were reinforced using tape or overlay to assure maximum exposure and absorption of drug. Samples for blood levels of lidocaine were collected before the application of the lidocaine patches (pre-dose on Day 8) and then in a serial manner at scheduled time points up to 48 hours (Day 10) after application of the lidocaine patches. After the patches were in place for 12 hours on Day 8, the patches were removed and the subjects completed a 7-day washout period. The subjects were confined to the clinic up to Day 10 and then returned to the clinic in the evening of Day 14 (+ 3 days).

Cohort 1, Part 3 – Lidocaine Patch 1.8% (Arm 2) or Lidoderm® 5% (Arm 1): Samples for assessment of blood levels of lidocaine (pre-lidocaine patch application) were collected on

Day 15. Then, on Day 15, subjects received an application of 3 patches or either lidocaine patch 1.8% or Lidoderm® 5% (whichever product was not applied in Part 2) for 12 hours to a defined area of normal skin on the back of the subjects. If necessary, the patches were reinforced using tape or overlay. Samples for blood levels of lidocaine were collected before application of the lidocaine patches (pre-dose) and then in a serial manner at scheduled time points up to 48 hours (Day 17) after application of the patches. Subjects remained in the clinic up to Day 17.

Safety and tolerability were evaluated by monitoring the occurrence of adverse events (AEs), local tolerability, changes in abbreviated physical examination findings, electrocardiogram (ECG) findings, vital signs (blood pressure and pulse rate) measurements, and clinical laboratory test results (biochemistry, hematology).

Cohort 2: Eligible subjects were admitted to the study site on Day -1. On the morning of Day 1, heat treatment with a heating pad was applied to each subject's back for 15 minutes. Immediately after the heat treatment, 3 lidocaine patches (1.8%) were applied to a defined area of normal skin on the subject's back which remained in place for 12 hours.

If necessary, the patches were reinforced using tape or overlay to assure maximum exposure and absorption of drug. Blood samples for the determination of lidocaine plasma concentrations were collected before the application of lidocaine patch (pre-dose on Day 1) and then in a serial manner at scheduled time points up to 48 hours (Day 3) after application of the lidocaine patches. After the patches were removed at the 12-hour post-application time point on Day 1, the subjects completed a 7-day washout period. The subjects were confined in the clinic up to Day 3 and then returned to the clinic in the evening on Day 7 (+ 3 days).

On Day 8, the subjects completed an exercise regimen before the application of 3 lidocaine patches 1.8%. The subjects walked at a moderate pace on a treadmill for approximately 20 minutes. Approximately 5 minutes after completing the exercise, 3 lidocaine patches 1.8% were then applied for 12 hours to a defined area of normal skin on the back of subjects. If necessary, the patches were reinforced using tape or overlay to assure maximum exposure and absorption of drug. Samples for blood levels of lidocaine were collected before the application of the patches (pre-dose on Day 8) and then in a serial manner at scheduled time points up to 48 hours (Day 10) after application of the lidocaine patches. Subjects completed a 7-day washout period after the patches were removed at the 12 hour post-application time point on Day 8. Subjects were confined to the clinic up to Day 10 and then returned to the clinic in the evening on Day 14 (+ 3 days).

On Day 15, subjects had 3 lidocaine patches 1.8% applied to a defined area of normal skin on the back. If necessary, the patches were reinforced using tape or overlay. Samples for blood levels of lidocaine were collected before the application of the patches (pre-dose) and then in a serial

manner at scheduled time points up to 48 hours (Day 17) after application of the lidocaine patches. Subjects were confined to the clinic up to Day 17.

Safety and tolerability were evaluated by monitoring the occurrence of AEs, local tolerability, changes in abbreviated physical examination findings, ECG findings, vital signs (blood pressure and pulse rate) measurements, and clinical laboratory test results (biochemistry, hematology).

NUMBER OF SUBJECTS (PLANNED, ENROLLED, AND ANALYZED):

It was planned to enroll 64 subjects into Cohort 1 and 12 subjects into Cohort 2. Actual enrollment was 58 subjects in Cohort 1 and 14 subjects in Cohort 2. The pharmacokinetic concentration population comprised 70 subjects; the pharmacokinetic parameter population comprised 70 subjects; and the safety population comprised 72 subjects.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Eligible subjects were healthy males and non-pregnant, non-nursing females who were between the ages of 18 and 65 years, inclusive, who had laboratory test results that were within normal limits.

Excluded were subjects who were taking any drug treatment at the time of the study; had taken prescription medication within 14 days of study start; had used over-the-counter products within 7 days of study start; were using narcotics chronically; had participated in an investigational or patch study within 30 days of study start; had recently donated or lost plasma or whole blood; had a serious illness within 4 weeks of study start; or had a history or suspected history of any condition that, in the opinion of the investigator, could interfere with the study conduct or observation. Smokers and subjects with a body mass index (BMI) greater than 36 kg/m^2 were also excluded.

STUDY DRUG, DOSE, AND MODE OF ADMINISTRATION, BATCH/LOT NUMBER:

The investigational product was Lidocaine patch 1.8% (Lot LIDTI87) and was provided by the sponsor. Each patch of the investigational product contained 36 mg of Lidocaine USP.

DURATION OF TREATMENT:

Approximately 17 days, with a screening period of up to 28 days.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH/LOT NUMBER:

- Lidoderm® (lidocaine patch 5%; Lot 23048 and 23018), which was manufactured by Teikoku Seiyaku Company for Endo Pharmaceuticals Inc. Each adhesive patch contained 700 mg of lidocaine (50 mg per gram adhesive) in an aqueous base.
- Lidocaine IV (Lot 35-459-DK), which was supplied in pre-filled syringes (20 mg/mL or 100 mg/5 mL, 2% solution) and was manufactured by Hospira. Injections containing

20 mg/mL (2%) lidocaine hydrochloride contained sodium chloride 6 mg to adjust tonicity.

PHARMACOKINETICS AND STATISTICAL METHODS:

Cohort 1:

All PK parameters were summarized by treatment period, using mean, standard deviation, 95% confidence interval, minimum, median, and maximum.

In addition, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were the key PK parameters tested for bioequivalence between the two patch treatments and stratified in the following manner: all subjects and by age ($\geq$ 18 to $<$ 65 years and $\geq$ 65 years). For this, the log-transformed quantities were analyzed in a mixed effects analysis of variance model, with treatment, sequence, and period as fixed effects and subject within sequence as a random effect. Estimates of the difference between treatment least squares means were obtained from the model with 90% confidence intervals. These estimates and confidence intervals were back-transformed onto the original scale to provide estimates of the geometric means for each treatment, and of the ratio of the geometric means. By convention, if the 90% confidence interval of the ratio of geometric means was within 80% to 125%, then the two treatments were considered bioequivalent.

Apparent dose and absolute bioavailability were compared between the two patch treatments using analysis of variance of the untransformed data and stratified in the following manner: all subjects and by age ($\geq$ 18 to $<$ 65 years and $\geq$ 65 years); T_{max} and $T_{½}$ were compared pairwise among all 3 treatments using Kruskal-Wallis methods.

Mean and individual subject plasma concentration time curves were presented on both linear and semilogarithmic scales.

Cohort 2:

No formal statistical analysis was performed. Descriptive statistics for lidocaine plasma concentrations were calculated and compared for each application condition studied (heat, exercise, and normal) for the enrolled subjects who had adequate blood sample collection to generate the key PK parameters.

Mean and individual subject plasma concentration time curves were presented on both linear and semi-logarithmic scales.

PHARMACOKINETICS ASSESSMENT METHODS

Concentrations of lidocaine in plasma were measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The following PK parameters were derived

from the observed plasma concentration-time data: C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, K_e, $T_{1/2}$, apparent dose (D), and absolute bioavailability (BA).

SAFETY ASSESSMENT METHODS:

Safety and tolerability were evaluated by monitoring the occurrence of adverse events (AEs), local tolerability, changes in abbreviated physical examination findings, electrocardiogram (ECG) results, vital signs (blood pressure and pulse rate) measurements, and clinical laboratory test results (biochemistry and hematology).

SUBJECT POPULATION:

A total of 58 subjects were enrolled in Cohort 1 and 56 (96.6%) completed the study. One subject discontinued because of an adverse event, and 1 subject withdrew consent. A total of 14 subjects were enrolled in Cohort 2 and all 14 subjects completed the study.

PHARMACOKINETICS RESULTS:

Key pharmacokinetic parameters for lidocaine 1.8% and Lidoderm® 5% are presented below.

Table 1 Key Pharmacokinetic Parameters and Calculation of Bioequivalence

(b) (4)

(b) (4)

[redacted]

Qualitatively, the effects of heat and exercise on the PK of 1.8% lidocaine patch were minimal. The overall shape and magnitude of the lidocaine concentration versus time profile curves for 1.8% lidocaine with heat, 1.8% lidocaine with exercise, and 1.8% lidocaine groups were similar, and geometric means for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} did not differ by more than 10% between the 3 groups.

Table 2 Comparison of $T_{1/2}$, T_{max}, and BA between Lidocaine 1.8% and Lidoderm® 5% Treatment Groups

(b) (4)

[redacted]

SAFETY RESULTS:

Lidoderm® 5% patch delivered the highest apparent dose of lidocaine (198.18 mg), as compared to 49.92 mg for the 1.8% lidocaine patch group and 57.02 mg for the 0.7 mg/kg IV bolus group.

Twelve subjects (20.7% of subjects) in Cohort 1 experienced a total of 17 AEs; 1 subject experienced an AE not related to study medication that led to study discontinuation. In Cohort 2, 5 subjects (35.7%) experienced a total of 7 AEs, none of which led to study discontinuation. All of the AEs in Cohort 1 and Cohort 2 were mild in intensity. There were no SAEs in either Cohort. The subject who discontinued was in the 0.7 mg/kg IV bolus lidocaine group. The subject experienced urticaria considered to be unrelated to study drug treatment and was discontinued from the study.

The overall incidence of treatment-related AEs in the lidocaine 1.8% group was similar to the currently marketed product Lidoderm® 5% group: 3.6% versus 3.5 %.

Small decreases in mean blood pressure and mean heart rate were observed in all 3 treatment groups in Cohort 1 at 1 hour post-dose that resolved by 4 hours post dose in the 1.8% and 5% Lidoderm® patch groups and by 24 hours in the IV 0.7 mg/kg lidocaine group. There were no other changes in vital signs noted in any treatment group.

CONCLUSION:

Lidocaine 1.8% patch was well-tolerated, with the overall incidence of treatment-related AEs similar to that of the Lidoderm® 5% group: 3.6% versus 3.5 %. All AEs were mild in intensity. There were no SAEs during the study.

(b) (4)

Qualitatively, the effects of heat and exercise on the PK of 1.8% lidocaine patch were minimal as compared to the normal application evaluated in Cohort 2.

DATE OF REPORT:

27-April-2015

Sponsor's Response on Jan 11, 2016:

Calculate the absolute dose of lidocaine absorbed from your product and the reference product, Lidoderm® patch 5%, using the method discussed in the response to your questions dated February 24, 2012, compare with Lidoderm® labeling, and provide justification how your data will establish PK bridging between your product and Lidoderm.

(b) (4)

Summary of Pharmacokinetic Parameter Values for Lidocaine IV Bolus (0.7 mg/kg), Lidocaine Patch 1.8%, and Lidoderm® Patch 5% Stratified (Study SCI-LIDO-PK-001)

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(b) (4)

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/s/

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