CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207962Orig1s000

STATISTICAL REVIEW(S)

US Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics
Division of Biometrics VI

STATISTICAL REVIEW AND EVALUATION

NDA NO.	207962
SERIAL NO.	
DATE RECEIVED BY THE CENTER	8/28/2017
DRUG NAME	ZTlido (lidocaine patch 1.8%)
DOSAGE FORM	TDS
INDICATION	
SPONSOR	Scilex Pharmaceuticals Inc.
REVIEW FINISHED	12/26/2017
STATISTICAL REVIEWER	Chao Wang, Ph.D.
SECONDARY REVIEWER	Meiyu Shen, Ph.D.
PROJECT MANAGER	Steven Kinsley

Chao Wang, Ph.D., Mathematical Statistician, CDER/OTS/OB/DBVI
Meiyu Shen, PhD., Lead Mathematical Statistician, CDER/OTS/OB/DBVI

Concur: _____

Yi Tsong, Ph.D., Division Director, CDER/OTS/OB/DBVI

CC List:

Lillian Patrician, CDER/OTS/OB
Steven Kinsley, CDER/OPQ/OPRO/DRBPMI/RBPMBI

Contents

1 Statistical evaluation of evidence

1.1 Executive summary

The statistical reviewer evaluated the sponsor's in vivo adhesion data collected in the clinical study A15.0168 for NDA 207962. The adhesion data was collected from 54 patches, each worn by a subject. For each patch, adhesion was assessed by an investigator at hour 0, 3, 6, 9, and 12 after application.

Below are the main findings.

- The adhesion scores for all subjects are either 0 or 1, with 96% of 0's and and 4% of 1's, i.e., at least 75% adhesion for all observed patches at all times, implying that the probability of a patch having at least 75% adhesion within 12 hours of application is 1 with 95% lower confidence limit 94.6%.
- The point estimate of the proportion of subjects having at least 90% adhesion, i.e., adhesion score being 0 , throughout the study, is 87.04% with 95% lower confidence limit 79.52%.
- At each of 0, 3, 6, 9, 12 hour, the point estimate of the probability of a patch having adhesion score 0 point is greater than 90%. However, the 95% lower confidence limit is below 90% at hour 9 and hour 12.
- We recommend the following criteria for assessing patch adhesion. For a given significance level $\alpha = 0.05$, the probability of a patch maintaining at least 90% and 75% adhesion throughout the entire wear period should be at least 75% and 90% respectively. This requires the 95% lower confidence limits for the probability of a patch maintaining at least 90% and 75% adhesion be greater than 75% and 90% respectively. The in vivo adhesion data support that this product passes the criteria.

1.2 Introduction

On 8/28/2017, FDA Office of Pharmaceutical Quality, Office of New Drug Products requested the Division of Biometrics VI, Office of Biostatistics to evaluate the sponsor's in vivo adhesion data of the transdermal delivery system (TDS), ZTlido, in the clinical study, A15.0168, in NDA 207962.

The study was an open label, single-treatment, single-period, single-application, adhesion performance study in healthy adult human subjects. The objective of this study was to evaluate the adhesion performance of ZTlido, Scilex Pharmaceuticals, Inc. Lidocaine Patch 36 mg/Patch (1.8%), monitor the adverse events and ensure the safety of the subjects. In this review, the statistical reviewers focused on evaluating adhesion performance.

The adhesion analysis included all patches from 54 subjects. No patch was removed early for unacceptable irritation and no subject dropped out of the study before the end of the 12-hour application. Adhesion was assessed at hour 0, 3, 6, 9, and 12 according to the following scoring system as recommended in the FDA guidance, *Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs* :

- 0: $\geq 90\%$ adhered (essentially no lift off the skin),
- 1: $\geq 75\%$ to $< 90\%$ adhered (some edges only lifting off the skin),
- 2: $\geq 50\%$ to $< 75\%$ adhered (less than half of the TDS lifting off the skin),
- 3: $> 0\%$ to $< 50\%$ adhered (not detached, but more than half of the TDS lifting off the skin without falling off),
- 4: $= 0\%$ adhered (TDS detached; completely off the skin).

Below, we evaluated and reviewed the sponsor's in vivo adhesion data and analysis.

1.3 Comments on the sponsor's analysis

The sponsor stated in their report that 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) +3, +6, +9, and +12 hours after application). However, the CAS is not meaningful in determining adhesion since different combination of adhesion scores could yield the same CAS.

The sponsor claimed that "greater than 90% of subjects had $\geq 90\%$ adhesion". However, our analysis showed that the claim is not correct.

1.4 Statistical reviewer's comments

First, we observed that all scores for all patches were either 0 or 1, indicating all patches maintained at least 75% adhesion throughout the study.

To assess whether greater than 90% of subjects have $\geq 90\%$ adhesion, we calculated the maximum adhesion score per subject. The distribution of the within-subject maximum score is shown in Table 1, which shows that the point estimate of the proportion of subjects having $\geq 90\%$ adhesion is 0.87 with 95% lower confidence limit 0.8.

Maximum score	0	1
Count	47	7
Empirical probability	0.87	0.13

Table 1: Summary of within-subject maximum adhesion score.

We also considered patch adhesion for all subjects at individual time points. For each time point, the point estimate and 95% lower confidence limits of a patch having score 0 are reported in Table 2, which shows that the point estimate probability of a patch having at least 90% adhesion at given time point are all greater than 90%. However, the 95% lower confidence limit is below 90% at hour 9 and hour 12.

Time point	0	3	6	9	12
Point estimate	1.00	0.96	0.96	0.94	0.91
95% lower confidence limit	1.00	0.92	0.92	0.89	0.84

Table 2: Summary of the estimates for probability of a patch having adhesion score 0 evaluated at different time points.

It may be impractical to require that a patch maintain at least 90% of adhesion during the entire wear period as patch adhesion will likely deteriorate over time. Furthermore, a patch with less adhesion, say, at least 75% adhesion, may also be acceptable. Thus we consider a functional criteria so that the probability of a patch with at least s% adhesion should increase as s decreases. We recommend that for a given significance level $\alpha = 0.05$, the probability of a patch maintaining at least 90% and 75% adhesion throughout the entire wear period should be at least 75% and 90% respectively. This requires the 95% lower confidence limits for the probability of a patch maintaining at least 90% and 75% adhesion be greater than 75% and 90% respectively.

The above analysis showed that the 95% lower confidence limit for the probability of a patch with at least 90% adhesion is 79.52%. Consider the probability of at least 75% adhesion. The data shows that the adhesion scores for all subjects are either 0 or 1, i.e., at least 75% adhesion for all observed patches at all times. Thus, the probability of a patch having at least 75% adhesion is estimated to be 1. Its 95% lower confidence limit cannot be calculated by normal approximation as the variance estimate is 0. We propose to use the following approach. Suppose that the true probability of at least 75% adhesion is p_1, then given n patches, the probability of the event E that all n independent patches maintain at least 75% adhesion is p_1^n, which is an increasing function of p_1. When p_1 is small enough, then the probability of observing E will be smaller than α. Thus $\alpha^{1/n}$ can be used as 95% lower confidence limit, which is 94.6% in this case. In summary, the patch data support that this product passes the preceding criteria.

1.5 Conclusion and Recommendation

In conclusion, we identified the following facts:

- The adhesion scores for all subjects were either 0 or 1, with 96% of 0's and and 4% of 1's, implying that the probability of a patch maintaining at least 75% adhesion during the entire wear period is 1 with 95% lower confidence limit 94.6%.
- The point estimate of the proportion of subjects having $\geq$ 90% adhesion throughout the study is 87.04% with 95% lower confidence limit 79.52%, which do not support the sponsor's claim that "greater than

90% of subjects had $\geq$ 90% adhesion".

- At each of 0, 3, 6, 9, 12 hour, the point estimate of the probability of a patch having at least 90% adhesion is greater than 90%. However, the 95% lower confidence limit is below 90% at hour 9 and 12.

We recommend the following criteria. For given significance level $\alpha = 0.05$, the probability of a patch maintaining at least 90% and 75% adhesion throughout the entire wear period should be at least 75% and 90% respectively. This requires the 95% lower confidence limits for the probability of a patch maintaining at least 90% and 75% adhesion be greater than 75% and 90% respectively. The in vivo adhesion data support that this product passes the criteria.

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

/s/

CHAO WANG
12/29/2017

YI TSONG
12/29/2017