# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 203567Orig1s000

# STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

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|---|---|
| **NDA/Serial Number:** | 203567 / 000 (Resubmission) |
| **Drug Name:** | Jublia (efinaconazole) solution 10% |
| **Indication(s):** | Onychomycosis |
| **Applicant:** | Dow |
| **Dates:** | Submitted: 12/20/2013<br>PDUFA: 6/20/2014 |
| **Review Priority:** | Resubmission (Class 2) |
| **Biometrics Division:** | Division of Biometrics III |
| **Statistics Reviewer:** | Kathleen Fritsch, Ph.D. |
| **Concurring Reviewer:** | Mohamed Alosh, Ph.D. |
| **Medical Division:** | Division of Dermatology and Dental Products |
| **Clinical Team:** | Gary Chiang, M.D. / David Kettl /M.D. |
| **Project Manager:** | Strother Dixon |

**Keywords:** Labeling review

# 1 Regulatory Background

NDA 203567 for Jublia (efinaconazole) solution 10% for the treatment of onychomycosis was originally submitted on 7/26/2012. The NDA received a Complete Response due to Product Quality issues. These issues were:

1. Inadequate manufacturing process and control information of the filling/capping/ (b) (4) operation.
2. Inadequate specification for the drug product.
3. Inadequate integrity of the container closure system.
4. Inadequate stability data to assure the expiration dating period.

With this submission, the applicant has submitted information to address the Product Quality issues. A complete biostatistical review was conducted during the initial review cycle. There were no biostatistical issues raised in the initial review that would preclude the conclusion that efficacy had been established in the clinical trials. The team has determined that the changes in the manufacturing and control will not necessitate any new clinical trials. Thus the conclusions from the initial biostatistical review are still applicable. The remaining biostatistical issue that was not addressed in the initial review cycle was product labeling. This review will provide biostatistical recommendations on the product labeling.

# 2 Biostatistical Conclusions from the Original Review Cycle

The following is the Executive Summary from the biostatistical review for the original review cycle for Jublia. (Reviewer Kathleen Fritsch, dated 3/5/2013).

> **Executive Summary**
> Efinaconazole solution 10% was superior to vehicle in the treatment of onychomycosis in two studies. Studies P3-01 and P3-02 enrolled subjects age 18 to 65 with a clinical diagnosis of onychomycosis and positive mycology. Subjects applied treatment once daily for 48 weeks. The primary efficacy endpoint was complete cure at Week 52 (0% clinical involvement of target toenail plus negative KOH and negative culture). The secondary efficacy endpoints specified in the protocol were: (1) clinical efficacy rate at Week 52 (<10% affected target nail area), (2) mycological cure rate at Week 52 (negative KOH and culture), and (3) unaffected new nail growth at Week 52 (change from baseline in healthy target nail measurement). Secondary endpoints were analyzed in sequential order. The primary and secondary efficacy endpoints were all statistically significant and the results are presented in Table 1.

**Table 1 – Primary and Secondary Efficacy Endpoints at Week 52 (SAP 1)**

| | Study P3-01 | | | Study P3-02 | | |
|---|---|---|---|---|---|---|
| | Efinacon. N = 656 | Vehicle N = 214 | p-value | Efinacon. N = 580 | Vehicle N = 201 | p-value |
| Complete Cure | 117 (17.8%) | 7 (3.3%) | <0.001 | 88 (15.2%) | 11 (5.5%) | <0.001 |
| Clinical Efficacy | 234 (36%) | 25 (12%) | <0.001 | 180 (31%) | 24 (12%) | <0.001 |
| Mycologic Cure | 362 (55%) | 36 (17%) | <0.001 | 310 (53%) | 34 (17%) | <0.001 |
| Unaffected new growth (mm) | 5.0 (0.2) | 1.6 (0.4) | <0.001 | 3.8 (0.2) | 0.9 (0.4) | <0.001 |

The applicant created two versions of the Statistical Analysis Plan (SAP). The first version of the SAP was signed off about a week after the last subject completed Study P3-01 and the proposed analyses were consistent with the endpoints and analyses specified in the protocol. However, the applicant then revised the SAP about 5 weeks later. The second version of the SAP redefined the sets of secondary and supportive endpoints, and the order in which they were to be analyzed. The primary endpoint remained the same in both versions of the SAP, and thus the primary conclusions of the study are not affected by the changes to the SAP. This review will focus on the endpoints pre-specified in the protocol (and the first version of the SAP), rather than those specified only in the second version of the SAP. The secondary endpoints specified in the second version of the SAP were only proposed after the studies were completed. Although the applicant maintains that the studies were still blinded at that time the second SAP was written, changing endpoints after the studies are completed raises the concern that the Type I error rate could be inflated. Note that because all of the proposed secondary endpoints from either version of the SAP had p-values <0.001, the analyses from the second version of the SAP would lead to the same conclusions of efficacy as those from the original protocol/first version of the SAP.

# 3 Applicant's Proposed Labeling

The following is the applicant's proposed labeling for the Clinical Studies Section (submission dated 1/16/2014).

**14 CLINICAL STUDIES**

The safety and efficacy of once daily use of JUBLIA for the treatment of onychomycosis of the toenail were assessed in two (b) (4) 52-week prospective, multi-center, randomized, (b) (4) studies in patients 18 years and older (18 to 70 years of age) with 20% to 50% clinical involvement of the area of the target toenail, without dermatophytomas or lunula (matrix) involvement. (b) (4) The (b) (4) compared 48-weeks of treatment with JUBLIA to the vehicle solution. (b) (4)


# 4 Recommendations Regarding the Applicant's Proposed Labeling

The key biostatistical recommendations regarding the applicant's proposed labeling are:

1. Present data from the two studies (b) (4) because efficacy is established in the individual studies.
2. Do not include the proposed (b) (4)
3. Present (b) (4) together in one table, selecting the clinically relevant and statistically supported secondary endpoints.

The following is this reviewer's recommended wording for the Clinical Studies section of labeling. Note that the final wording is not final, and may change.

**14 CLINICAL STUDIES**

The safety and efficacy of once daily use of JUBLIA for the treatment of onychomycosis of the toenail were assessed in two 52-week prospective, multi-center, randomized, double-blind clinical trials in patients 18 years and older (18 to 70 years of age) with 20% to 50% clinical involvement of the area of the target toenail The trials compared 48-weeks of treatment with JUBLIA to the vehicle solution. The Complete Cure rate was assessed at Week 52 (4-weeks after completion of therapy). Complete cure is defined as 0% involvement of the target nail (no clinical evidence of onychomycosis of the target toenail) in addition to Mycologic Cure, defined as both negative fungal culture and negative KOH. Table 2 lists the efficacy results for trials 1 and 2.

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