An Open-label Study Evaluating the Long-term Efficacy, Quality of Life, and Safety of Lidose-Isotretinoin (ABSORICA®) Capsules Administered Without Food in Patients With Severe Recalcitrant Nodular Acne: Interim Analysis of 20-Week Active Treatment Period

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BACKGROUND

- Severe acne is known to have a significant adverse effect on self-esteem and quality of life (QOL).[1] Effective treatment of acne, with isotretinoin, can subsequently improve the patient's QOL. The timing of QOL improvement over the course of treatment with lidose-isotretinoin has not been established
- Isotretinoin products must be taken with a high-fat meal to achieve optimal absorption. Fasted plasma levels of isotretinoin can be nearly 60% lower than fed levels.[2] Noncompliance with the food intake requirements can potentially compromise the long-term efficacy of isotretinoin[3]
- Absorption of lidose-isotretinoin is less dependent on the amount and/or type of food intake and it can be taken without meals, while still providing a reliable isotretinoin blood concentration[4]

OBJECTIVE

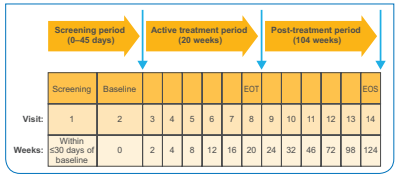
- To evaluate the efficacy and safety of lidose-isotretinoin taken without food by patients with severe recalcitrant nodular acne, in addition to assessing their quality of life
  - Primary objective during the 20-week active treatment period (ATP) was to evaluate the QOL of patients taking lidose-isotretinoin twice daily (bid) without food
  - Secondary objectives during the ATP were to evaluate the efficacy and safety of lidose-isotretinoin taken bid without food

METHODS

Study Design

- This is a phase 4, multicenter, single-arm, open-label study conducted in the United States in patients with severe recalcitrant nodular acne (NCT02457520, **Figure 1**) consisting of 2 phases: a 20-week (5-month) open-label ATP and a 104-week (2-year) post-treatment period

Figure 1. Study Design



EOS=end of study; EOT=end of treatment.

Study Population

- Key inclusion criteria included:
  - 12–45 years of age
  - Recalcitrant acne severe enough for isotretinoin treatment, including ≥5 facial nodules
  - No prior exposure to systemic isotretinoin or other systemic retinoid
  - Weight 40–110 kg
  - Women must not be pregnant and must not be breastfeeding; female patients of childbearing potential must use 2 forms of effective contraception simultaneously for 1 month before trial, during trial, and for 1 month after stopping study medication or commit to continuous abstinence from heterosexual intercourse, and have a negative serum pregnancy test

Treatment

- Dosing during 20-week ATP to attain target cumulative dose of 120–150 mg/kg:
  - 0.5 mg/kg/day divided into 2 daily doses for 4 weeks followed by
  - 1.0 mg/kg/day divided into 2 daily doses for 16 weeks
- Study medication was taken without food (1 hour before or at least 2 hours after ingestion of food/beverages other than water)

Endpoints

- Primary efficacy endpoint was the change from baseline to the end of treatment (EOT) in the Acne-QOL score, assessed on a graded scale (overall and by domain)
  - Domains included self-perception, role-social, role-emotional, and acne symptoms
- Secondary efficacy endpoints included monthly change from baseline in Acne-QOL scores (overall and by domain) and lesion counts during the ATP and change from baseline to EOT in Investigator's Global Assessment (IGA) scores

Statistical Analysis

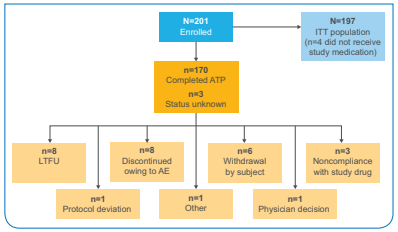
- Efficacy evaluation was conducted using the intent-to-treat population
- Overall Acne-QOL score, each domain score, and the changes from baseline for these scores were summarized using descriptive statistics. Differences between baseline and postbaseline values were analyzed using paired t-tests
- Descriptive statistics are provided for mean percentage change from baseline value for inflammatory, noninflammatory, and total lesion counts. Differences between baseline and postbaseline values were analyzed using paired t-tests
- Descriptive statistics are provided for IGA observed values

RESULTS

Disposition

- A total of 201 patients (mean age: 18.7 [range: 12–45] years) were enrolled in the study at 21 sites (**Figure 2**)
  - 85% (170/201) of patients completed the 20-week ATP

Figure 2. Patient Disposition



AE=adverse event; ATP=active treatment period; ITT=intent-to-treat; LTFU=lost to follow-up.

- Baseline demographics and disease characteristics are presented in **Tables 1** and **2**

Table 1. Baseline Demographics

	All Patients Enrolled (N=201)
Gender, n (%)	
Male	125 (62.2)
Female	76 (37.8)
Race, n (%)	
American Indian or Alaska native	3 (1.5)
Asian	8 (4.0)
Black or African American	17 (8.5)
Multiple	1 (0.5)
Native Hawaiian or other Pacific islander	1 (0.5)
Other	4 (2.0)
White	167 (83.1)
Ethnicity, n (%)	
Hispanic or Latino	31 (15.4)
Age, y	
Mean (SD)	18.7 (6.4)
Range	12–45

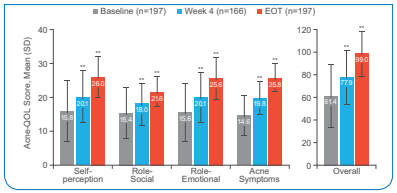
Table 2. Baseline Disease Characteristics

	Intent-to-Treat Population (N=197)
Number of inflammatory lesions	
Mean (SD)	33.8 (17.0)
Median (range)	32 (5–108)
Number of noninflammatory lesions	
Mean (SD)	40.1 (41.3)
Median (range)	27 (0–250)
Investigator's Global Assessment score	
Mean (SD)	4.1 (0.5)
Median (range)	4 (3–5)

Efficacy

- There was a significant increase in mean (SD) Acne-QOL from baseline to EOT (61.4 [28.4] vs 99.0 [19.8], $P<0.0001$). All 4 domains (self-perception, role-social, role-emotional, acne symptoms) were significantly improved over the course of treatment, with positive improvements beginning at Week 4 (**Figure 3**)

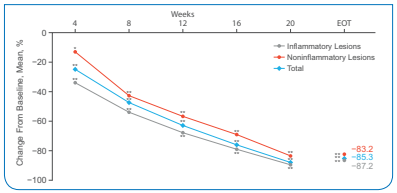
Figure 3. Improvement in Acne-QOL Scores at Week 4 and EOT



EOT values reflect the last visit for which a subject had data in the ATP. **P≤0.0001.
ATP=active treatment period; EOT=end of treatment; QOL=quality of life.

- Mean (SD) percentage change in inflammatory (–87.2 [22.5]) and noninflammatory lesion (–83.2 [30.3]) counts from baseline to EOT were significant ($P<0.0001$) (**Figure 4**)

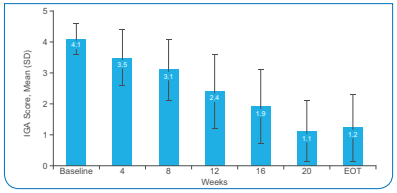
Figure 4. Mean Change in Lesion Counts From Baseline to EOT



EOT values reflect the last visit for which a subject had data in the ATP. Differences between postbaseline and baseline values analyzed using paired t-tests. *P=0.0002; **P≤0.0001.
ATP=active treatment period; EOT=end of treatment.

- Mean IGA scores improved from baseline by approximately 3.0 points at EOT (**Figure 5**)

Figure 5. IGA Scores Over Time From Baseline to EOT



EOT values reflect the last visit for which a subject had data in the ATP.
ATP=active treatment period; EOT=end of treatment; IGA=Investigator's Global Assessment.

Safety

- A total of 286 adverse events (AEs) was reported in 60.2% of patients (121/201)
  - The most common AEs were dry skin (10.9%), dry lips (10.4%), and cheilitis (9.0%)
- A total of 166 treatment-related AEs was reported in 46.3% of patients (93/201)
  - The most commonly reported were dry lips (10.4%), dry skin (10.4%), and cheilitis (9.0%)
- Twelve severe AEs were reported; 5 were considered to be treatment related
  - Nausea (n=2), increased blood cholesterol (n=1), liver function test abnormal (n=1), and headache (n=1)
- Psychiatric AEs occurred in 17 patients (8.5%). The psychiatric events reported in more than 1 patient were depression (4.0%), insomnia (1.0%), and anxiety (1.0%)
- Abnormal laboratory results occurred in 11 patients (5.5%); those reported in more than 1 patient were blood triglycerides increased (3.5%), increased alanine aminotransferase (1.5%), increased aspartate aminotransferase (1.5%), and blood cholesterol increased (1.5%)
- One serious AE was reported: diabetes mellitus on study Day 127, severe in intensity and unlikely related to study treatment
- Eight patients discontinued the study owing to AE
  - Psychiatric events (n=5) and abnormalities in laboratory test results (n=3)
  - Six additional patients had study drug withdrawn for an AE: psychiatric events (n=4), migraine (n=1), and diabetes mellitus (n=1)

CONCLUSIONS

- Twice-daily use of lidose-containing isotretinoin taken without food improved patients' QOL over the 20-week treatment period, with improvement seen as early as Week 4
- Clinical efficacy was also demonstrated
- AEs were generally consistent with the known safety profile for isotretinoin

REFERENCES

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Lidose-isotretinoin is a retinoid indicated for the treatment of severe recalcitrant nodular acne in patients 12 years of age and older. AZ and JD consulted on the design and implementation of this clinical trial for Sun Pharmaceutical Industries, Inc., who sponsored the study and supported the development of this presentation.

DISCLOSURES

AZ has served as a consultant for Cassiopea and Ranbaxy/Sun Pharmaceutical Industries, Inc. **JD** has served as a consultant, speaker, and research investigator for Sun Pharmaceutical Industries, Inc.