Comparative Pharmacokinetic Profiles of a Novel Low-Dose Micronized-Isotretinoin 32-mg Formulation and Lidose-Isotretinoin 40 mg in Fed and Fasted Conditions: 2 Open-label, Randomized Crossover Studies in Healthy Adult Participants

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SYNOPSIS

- Lidose-isotretinoin 40 mg, unlike traditional isotretinoin, does not require administration with a high-fat, high-calorie meal to optimize bioavailability and efficacy because it is presolubilized in a lipid matrix[1,2]
- A novel low-dose Micronized-isotretinoin 32-mg formulation has been developed by adopting an optimized micronization technology that substantially increases the surface area per unit mass of the drug in formulation

OBJECTIVES

- To evaluate the bioavailability of Micronized-isotretinoin 32 mg compared with Lidose-isotretinoin 40 mg under fed and fasted conditions in healthy participants
- To assess the effect of food on the bioavailability of Micronized-isotretinoin 32 mg in healthy participants

METHODS

- This analysis includes data from 2 open-label, randomized crossover studies in healthy volunteers: the fed bioequivalence and food-effect study and the fasting study
- Eligible participants were healthy men (both studies) and women (fed bioequivalence and food-effect study only) ≥18 years of age with body mass index between 18 and 30 kg/m^2
  - Male participants were required to use a reliable form of contraception throughout the study, and female participants were required to be of nonchildbearing potential (defined as naturally postmenopausal [no menses] for at least 2 years before initial dosing with a documented follicle-stimulating hormone level ≥40 mIU/mL at screening or surgically postmenopausal/sterile [eg, bilateral oophorectomy, tubal ligation, or hysterectomy], with the procedure performed at least 6 months before initial dosing)
- Exclusion criteria for both studies included:
  - History of allergy or sensitivity to retinoids or vitamin A
  - Significant history or current evidence of chronic infectious disease system disorders or organ dysfunction
  - History or presence of gastrointestinal disease or inflammatory bowel disease or a history of malabsorption in the previous year
  - History (personal or family) of psychiatric disorders in the last 2 years requiring treatment or hospitalization
  - Presence of a medical condition requiring regular treatment with prescription drugs
  - History of excessive alcohol consumption or any drug or alcohol addiction that required treatment during the previous 12 months

Treatments

- Fed bioequivalence and food-effect study
  - Multicenter, 3-treatment, 3-period, 6-sequence crossover study in which participants were randomized to 1 of 6 possible sequences that each included 3 periods of treatment:
    - Fasted-state Micronized-isotretinoin 32 mg: a single dose of Micronized-isotretinoin 32 mg following an overnight fast (defined as no food or beverage intake other than water) of at least 10 hours
    - Fed-state Micronized-isotretinoin 32 mg: a single dose of Micronized-isotretinoin 32 mg following a standardized high-fat, high-calorie breakfast (2 fried eggs, 2 strips of bacon, 4 oz of hash browns, 2 slices of buttered toast, and 8 oz of whole milk; this Food and Drug Administration standard meal contained about 150 protein calories, 250 carbohydrate calories, and 500 fat calories) preceded by an overnight fast of at least 10 hours
    - Fed-state Lidose-isotretinoin 40 mg: a single dose of Lidose-isotretinoin 40 mg following a standardized high-fat, high-calorie breakfast preceded by an overnight fast of at least 10 hours
- Fasting study
  - Single-center, 2-treatment, 2-period, 2-sequence crossover study in which participants were randomized to 1 of 2 possible sequences that each included 2 periods of treatment:
    - Fasted-state Micronized-isotretinoin 32 mg: a single dose of Micronized-isotretinoin 32 mg following an overnight fast of at least 10 hours
    - Fasted-state Lidose-isotretinoin 40 mg: a single dose of Lidose-isotretinoin 40 mg following an overnight fast of at least 10 hours
- The interval between dosing was 21 days in both studies
- Blood samples were collected before dosing to establish endogenous isotretinoin levels and then at intervals over the 96 hours postdosing

Endpoints

- Fed bioequivalence and food-effect study
  - Relative bioavailability of Micronized-isotretinoin 32 mg compared with Lidose-isotretinoin 40 mg in the fed state
  - Effect of food on the bioavailability of Micronized-isotretinoin 32 mg
- Fasting study
  - Relative bioavailability of Micronized-isotretinoin 32 mg compared with Lidose-isotretinoin 40 mg in the fasted state
- In both studies, safety was determined by the evaluation of adverse events (AEs)

Statistical Analysis

- For all treatments, bioavailability was measured using baseline-adjusted log-transformed maximum isotretinoin plasma concentration (LnC_{max}) and baseline-adjusted log-transformed area under the plasma concentration-time curve from time 0 to last measurable isotretinoin concentration ($LnAUC_{0-t}$) and from time 0 to infinity ($LnAUC_{0-\infty}$)
  - For comparison of fed-state Micronized-isotretinoin 32 mg with fed-state Lidose-isotretinoin 40 mg, bioequivalence was determined if the 90% confidence intervals (CIs) on the least squares geometric mean (LSGM) ratios for each parameter fell within the 80.0%–125.0% range
  - Absorption rate in the fasted state was compared between Micronized-isotretinoin 32 mg and Lidose-isotretinoin 40 mg by post hoc partial area evaluation from dose to C_{max}, after C_{max} to 12 hours, and from 12 hours to 24 hours
- Analysis of variance was performed for both studies, testing 2 1-sided hypotheses at the α=0.05 level of significance using SAS® (SAS Institute Inc., Cary, NC, USA), with the general linear model procedure used for the fasting study and a mixed procedure used for the fed bioequivalence and food-effect study
- Data from participants with some missing data were used if pharmacokinetic parameters could be estimated using the remaining data points; otherwise, data from these participants were excluded from the final analysis

RESULTS

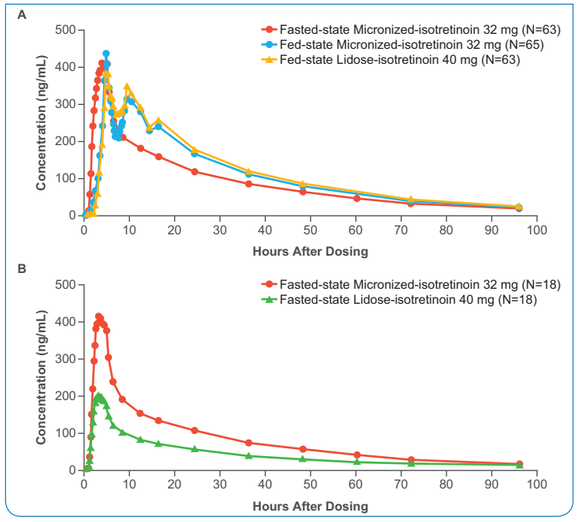
- In the fed bioequivalence and food-effect study, 71 participants enrolled and 65 were included in the analyses
  - Reasons for discontinuation were voluntary withdrawal (5 participants), positive substance abuse screen (2 participants), noncompliance with breakfast requirements (2 participants), and loss to follow-up (1 participant)
- In the fasting study, 18 participants enrolled and all were included in the analyses
- Baseline demographics for participants in both studies are presented in **Table 1**

Table 1. Baseline Demographics

	Fed Bioequivalence and Food-Effect Study			Fasting Study	
	Fasted-State Micronized-Isotretinoin 32 mg (N=63)	Fed-State Micronized-Isotretinoin 32 mg (N=65)	Fed-State Lidose-Isotretinoin 40 mg (N=63)	Fasted-State Micronized-Isotretinoin 32 mg (N=18)	Fasted-State Lidose-Isotretinoin 40 mg (N=18)
Sex					
Male	47 (74.6)	49 (75.4)	47 (74.6)	18 (100)	18 (100)
Female	16 (25.4)	16 (24.6)	16 (25.4)	0	0
Race					
Asian	2 (3.2)	2 (3.1)	2 (3.2)	0	0
Black	34 (54.0)	35 (53.9)	34 (54.0)	7 (38.9)	7 (38.9)
White	20 (31.8)	20 (30.8)	19 (30.2)	8 (44.4)	8 (44.4)
Hispanic	4 (6.4)	5 (7.7)	5 (7.9)	2 (11.1)	2 (11.1)
Other	3 (4.8)	3 (4.6)	3 (4.8)	1 (5.6)	1 (5.6)
Age, y					
Mean±SD	44.2±14.8	44.2±14.6	44.3±14.4	44.1±11.8	44.1±11.8
Median	38.0	38.0	38.0	43.5	43.5
Range	21–68	21–68	21–68	22–62	22–62
Weight, lb					
Mean±SD	169.4±27.0	169.5±27.2	169.9±27.6	175.3±28.1	175.3±28.1
Median	165.0	165.0	166.0	180.5	180.5
Range	90–225	90–225	90–225	133–232	133–232
BMI, kg/m^2					
Mean±SD	25.5±2.9	25.4±3.0	25.5±3.0	25.5±2.9	25.5±2.9
Median	26.1	26.1	26.1	24.9	24.9
Range	18.2–30.0	18.2–30.0	18.2–30.0	20.4–29.8	20.4–29.8
Tobacco user					
Yes	20 (31.8)	21 (32.3)	20 (31.8)	6 (33.3)	6 (33.3)
No	43 (68.3)	44 (67.7)	43 (68.3)	12 (66.7)	12 (66.7)

Data presented as n (%) unless otherwise stated.
BMI, body mass index; N, number of participants in the treatment group; n, number of participants of a particular demographic; SD, standard deviation.

Figure 1. Mean Baseline-Adjusted Plasma Isotretinoin Concentration vs Time Curves for (A) Fasted-State Micronized-Isotretinoin 32 mg, Fed-State Micronized-Isotretinoin 32 mg, and Fed-State Lidose-Isotretinoin 40 mg (Fed Bioequivalence and Food-Effect Study) and (B) Fasted-State Micronized-Isotretinoin 32 mg and Fasted-State Lidose-Isotretinoin 40 mg (Fasting Study)



- 90% CIs for the LSGM ratios for the baseline-adjusted $LnAUC_{0-t}$ (91.9%–98.4%), $LnAUC_{0-\infty}$ (91.5%–98.0%), and LnC_{max} (96.3%–112.6%) for fed-state Micronized-isotretinoin 32 mg vs fed-state Lidose-isotretinoin 40 mg all fell within the 80.0%–125.0% range for bioequivalence, showing that Micronized-isotretinoin 32 mg is bioequivalent to Lidose-isotretinoin 40 mg under fed conditions (**Table 2**, **Figure 1A**)
- Baseline-adjusted LSGM ratios for fasted-state Micronized-isotretinoin 32 mg vs fasted-state Lidose-isotretinoin 40 mg show that Micronized-isotretinoin 32 mg had approximately 2 times higher bioavailability than Lidose-isotretinoin 40 mg under fasted conditions (**Table 3**, **Figure 1B**)
  - Partial area evaluation indicates that fasted-state Micronized-isotretinoin 32 mg had higher absorption than fasted-state Lidose-isotretinoin 40 mg in each segment from dose to C_{max} ($LnAUC_{0-4}$ LSGM ratio: 164.8%), after C_{max} to 12 hours ($LnAUC_{4-12}$ LSGM ratio: 206.1%), and from 12 hours to 24 hours ($LnAUC_{12-24}$ LSGM ratio: 200.3%)
- Administering Micronized-isotretinoin 32 mg with a high-fat meal increased $LnAUC_{0-t}$ and $LnAUC_{0-\infty}$ by 24.8% and 23.2%, respectively, compared with administration in the fasted state, but had no effect on LnC_{max}, indicating that food minimally affects the extent but not the rate of Micronized-isotretinoin 32 mg absorption (**Table 4**, **Figure 1A**)
- Sixty-eight AEs were reported by 36 of the 71 participants in the fed bioequivalence and food-effect study: 34 occurred after administration of fasted-state Micronized-isotretinoin 32 mg, 16 after fed-state Micronized-isotretinoin 32 mg, and 18 after fed-state Lidose-isotretinoin 40 mg
  - Headache was the most frequently reported AE, reported by 6, 3, and 2 participants following administration of fasted-state Micronized-isotretinoin 32 mg, fed-state Micronized-isotretinoin 32 mg, and fed-state Lidose-isotretinoin 40 mg, respectively
- In the fasting study, 7 AEs were reported by 4 of the 18 participants (3 for fasted-state Micronized-isotretinoin 32 mg and 4 for fasted-state Lidose-isotretinoin 40 mg)
  - Oropharyngeal pain was the most frequently reported AE, occurring in 1 participant following administration of fasted-state Micronized-isotretinoin 32 mg and 1 participant following administration of fasted-state Lidose-isotretinoin 40 mg
- No serious AEs were reported in either study

CONCLUSIONS

- Micronized-isotretinoin 32 mg is bioequivalent to Lidose-isotretinoin 40 mg under fed conditions and is twice as bioavailable as Lidose-isotretinoin 40 mg under fasted conditions
- Food has no effect on the rate and a marginal effect on the extent of Micronized-isotretinoin 32 mg absorption, which is less than the effect on Lidose-isotretinoin 40 mg and other marketed isotretinoin products[3,4]

Table 2. Baseline-Adjusted Plasma Isotretinoin Concentrations for Fed-State Micronized-Isotretinoin 32 mg and Fed-State Lidose-Isotretinoin 40 mg (Fed Bioequivalence and Food-Effect Study)

Parameter	Treatment	Arithmetic Mean±SD (% CV)	LSGM	Participants Contrasted, n[a]	LSGM Ratio (%)	90% Confidence Interval (%)	*P*-Value Sequence
AUC_{0-t} (h·ng/mL)	Fed-state Micronized-isotretinoin 32 mg	10,209.1±1967.5 (19.3)	9915	61	95.07	91.88–98.36	0.1327
	Fed-state Lidose-isotretinoin 40 mg	10,693.0±2247.3 (21.0)	10,430				
$AUC_{0-\infty}$ (h·ng/mL)	Fed-state Micronized-isotretinoin 32 mg	10,921.9±2176.1 (19.9)	10,654	61	94.71	91.51–98.02	0.1940
	Fed-state Lidose-isotretinoin 40 mg	11,676.6±2851.0 (24.4)	11,249				
C_{max} (ng/mL)	Fed-state Micronized-isotretinoin 32 mg	645.7±275.2 (42.6)	596.7	63	104.09	96.27–112.55	0.4744
	Fed-state Lidose-isotretinoin 40 mg	595.7±183.8 (30.9)	573.2				

[a]Number of participants contrasted represents the number of participants who had data for this parameter in each treatment group.
AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the last measurable concentration; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; C_{max}, maximum measured plasma concentration; CV, coefficient of variation; LSGM, least squares geometric mean; SD, standard deviation.

Table 3. Baseline-Adjusted Plasma Isotretinoin Concentrations for Fasted-State Micronized-Isotretinoin 32 mg and Fasted-State Lidose-Isotretinoin 40 mg (Fasting Study)

Parameter	Treatment	Arithmetic Mean±SD (% CV)	LSGM	Participants Contrasted, n[a]	LSGM Ratio (%)	90% Confidence Interval (%)	*P*-Value Sequence
AUC_{0-t} (h·ng/mL)	Fasted-state Micronized-isotretinoin 32 mg	7485.1±1693.9 (22.6)	7289	18	198.62	175.19–225.17	0.9168
	Fasted-state Lidose-isotretinoin 40 mg	3833.6±1160.7 (30.3)	3670				
$AUC_{0-\infty}$ (h·ng/mL)	Fasted-state Micronized-isotretinoin 32 mg	8016.3±1800.4 (22.5)	7807	18	196.33	172.86–222.98	0.7367
	Fasted-state Lidose-isotretinoin 40 mg	4164.2±1294.4 (31.1)	3977				
C_{max} (ng/mL)	Fasted-state Micronized-isotretinoin 32 mg	539.0±180.3 (33.5)	507.6	18	219.63	187.26–257.60	0.4234
	Fasted-state Lidose-isotretinoin 40 mg	238.2±60.8 (25.5)	231.1				

[a]Number of participants contrasted represents the number of participants who had data for this parameter in each treatment group.
AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the last measurable concentration; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; C_{max}, maximum measured plasma concentration; CV, coefficient of variation; LSGM, least squares geometric mean; SD, standard deviation.

Table 4. Baseline-Adjusted Plasma Isotretinoin Concentrations for Fasted-State Micronized-Isotretinoin 32 mg and Fed-State Micronized-Isotretinoin 32 mg (Fed Bioequivalence and Food-Effect Study)

Parameter	Treatment	Arithmetic Mean±SD (% CV)	LSGM	Participants Contrasted, n[a]	LSGM Ratio (%)	90% Confidence Interval (%)	*P*-Value Sequence
AUC_{0-t} (h·ng/mL)	Fasted-state Micronized-isotretinoin 32 mg	8466.3±2458.2 (29.0)	8042	63	124.84	117.29–132.88	0.0351
	Fed-state Micronized-isotretinoin 32 mg	10,209.1±1967.5 (19.3)	10,039				
$AUC_{0-\infty}$ (h·ng/mL)	Fasted-state Micronized-isotretinoin 32 mg	9219.1±2782.1 (30.2)	8711	62	123.24	115.93–131.01	0.0600
	Fed-state Micronized-isotretinoin 32 mg	10,921.9±2176.1 (19.9)	10,736				
C_{max} (ng/mL)	Fasted-state Micronized-isotretinoin 32 mg	611.3±285.2 (46.6)	539.4	63	108.25	94.42–124.12	0.2908
	Fed-state Micronized-isotretinoin 32 mg	645.7±275.2 (42.6)	583.9				

[a]Number of participants contrasted represents the number of participants who had data for this parameter in each treatment group.
AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the last measurable concentration; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; C_{max}, maximum measured plasma concentration; CV, coefficient of variation; LSGM, least squares geometric mean; SD, standard deviation.

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DISCLOSURES

SM and **SK** are employees of Sun Pharmaceutical Industries Ltd. **JS** is an employee of Sun Pharmaceutical Industries, Inc.

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