A Prospective, Multicenter, Randomized, Double-blind, Vehicle-controlled Phase 2 Study to Evaluate the Safety and Efficacy of a Combination Of 3% Minocycline and 0.3% Adapalene Topical Foam Formulation for the Treatment of Moderate-to-Severe Acne

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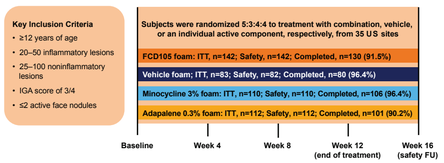
Introduction

- Acne vulgaris is a common disease of both males and females, usually manifesting initially during adolescence and affecting most of the population at some point during their lifetime[1-3]
- Acne is frequently treated with antibiotics, retinoids, or both[1,4]
  - Minocycline is a second-generation tetracycline with bacteriostatic and anti-inflammatory properties[2,5]
  - Adapalene is a third-generation retinoid that has anti-inflammatory and comedolytic properties, and normalizes keratinization[1]
- A fixed combination of minocycline 3% and adapalene 0.3%, FCD105, has been developed as a novel topical foam for the treatment of moderate-to-severe acne
  - Both of these molecules are used individually or in combination with other agents (eg, benzoyl peroxide) in FDA-approved treatments for acne although a retinoid/tetracycline topical formulation had not been evaluated in clinical studies prior to this study and may offer an improved treatment option for patients with moderate-to-severe acne
- **The objectives of this study are:**
  - To evaluate the safety, tolerability, and efficacy of the combination product FCD105 in the treatment of moderate-to-severe acne vulgaris with up to 12 weeks of daily treatment, in comparison with vehicle
  - To compare the efficacy and safety of FCD105 against the individual, active-drug components: minocycline 3% and adapalene 0.3% topical foam products

Methods

- Study FX2016-40 was a randomized, multicenter, double-blind, vehicle-controlled, Phase 2 study
  - The purpose was to evaluate the safety, tolerability, and efficacy over a 12-week treatment period of FCD105 as compared with vehicle foam and the individual active components of FCD105 in the treatment of subjects with moderate-to-severe acne vulgaris in a 2x2 factorial design (**Figure 1**)
- Study drug administration
  - Subjects were randomized 5:3:4:4 to one of the following 4 color-matched foam treatments: FCD105 (minocycline 3% + adapalene 0.3%), vehicle, minocycline 3%, or adapalene 0.3%
    - Overall, there was high rate of study completion; 417 (93.3%) of the 447 subjects who were included in the ITT population completed the study, with comparable completion rates between treatment groups (**Figure 1**)
  - The assigned study treatment was applied once daily for 12 weeks
- Co-primary efficacy endpoints
  - Absolute change in inflammatory and noninflammatory lesion counts from baseline to week 12 for FCD105 vs. vehicle
  - Percent of subjects achieving IGA treatment success at week 12, where success was defined as a score of 0 (clear) or 1 (minimal) and a ≥2-grade improvement (decrease) from baseline for FCD105 vs. vehicle
- Secondary efficacy endpoints
  - Percentage change of inflammatory and noninflammatory lesion count for FCD105 vs vehicle at weeks 4, 8, and 12
  - Absolute change of inflammatory and noninflammatory lesion count for FCD105 vs minocycline 3% and FCD105 vs. adapalene 0.3% from baseline to week 12
  - Percent of patients achieving IGA treatment success at week 12 for FCD105 vs minocycline 3% and FCD105 vs. adapalene 0.3%
- Safety evaluations
  - Treatment-emergent adverse events, local skin tolerability assessments, vital signs, and physical examinations
- A subject satisfaction questionnaire was completed at baseline and week 12

Figure 1. Study design



IGA=Investigator's Global Assessment, based upon a 5-point scale in which 0=clear, 1=minimal, 2=mild, 3=moderate, and 4=severe; FU, follow-up; ITT=intent-to-treat.

Results

Baseline Demographics and Disease Characteristics (ITT Population)

- Baseline demographics and disease characteristics were similar across treatment groups (**Table 1**)
- The majority of subjects were white (70.7%) and female (61.1%); mean age was 21.3 years
- The average inflammatory and noninflammatory lesion counts across groups at baseline were 30.6 and 48.1, respectively; the majority of subjects (90.8%) had moderate (IGA=3) disease severity at baseline

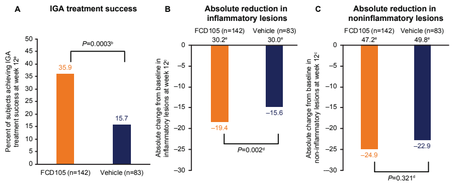
Table 1. Baseline demographics and disease characteristics (ITT Population)

Variable	FCD105 (n=142)	Vehicle (n=83)	Minocycline 3% (n=110)	Adapalene 0.3% (n=112)	Overall (N=447)
Age (years), mean (SD)	21.0 (7.05)	21.4 (7.25)	20.8 (8.28)	22.0 (7.98)	21.3 (7.63)
Age groups, n (%)					
<18 years	64 (45.1)	32 (38.6)	55 (50.0)	41 (36.6)	192 (43.0)
18–40 years	76 (53.5)	50 (60.2)	52 (47.3)	70 (62.5)	248 (55.5)
41–64 years	2 (1.4)	1 (1.2)	3 (2.7)	1 (0.9)	7 (1.6)
Sex, n (%)					
Male	62 (43.7)	33 (39.8)	43 (39.1)	36 (32.1)	174 (38.9)
Female	80 (56.3)	50 (60.2)	67 (60.9)	76 (67.9)	273 (61.1)
Ethnicity, n (%)					
Hispanic or Latino	63 (44.4)	33 (39.8)	47 (42.7)	43 (38.4)	186 (41.6)
Not Hispanic or Latino	79 (55.6)	50 (60.2)	63 (57.3)	69 (61.6)	261 (58.4)
Race, n (%)					
America Indian or Alaska Native	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Asian	7 (4.9)	6 (7.2)	5 (4.5)	2 (1.8)	20 (4.5)
Black or African American	29 (20.4)	15 (18.1)	23 (20.9)	27 (24.1)	94 (21.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	1 (0.2)
White	103 (72.5)	56 (67.5)	81 (73.6)	76 (67.9)	316 (70.7)
Multiple	0 (0.0)	4 (4.8)	0 (0.0)	4 (3.6)	8 (1.8)
Not reported	2 (1.4)	1 (1.2)	1 (0.9)	3 (2.7)	7 (1.6)
Inflammatory lesion count, mean (SD)	30.2 (7.6)	30.0 (8.1)	31.0 (8.7)	31.1 (8.6)	30.6 (8.2)
Noninflammatory lesion count, mean (SD)	47.2 (16.7)	49.8 (16.5)	48.4 (19.1)	47.8 (16.9)	48.1 (17.3)
IGA score					
Moderate (IGA=3)	134 (94.4)	76 (91.6)	96 (87.3)	100 (89.3)	406 (90.8)
Severe (IGA=4)	8 (5.6)	7 (8.4)	14 (12.7)	12 (10.7)	41 (9.2)

Efficacy Data

- FCD105 showed a statistically significant improvement compared with vehicle for the co-primary endpoints of IGA treatment success (**Figure 2A**) and absolute change in inflammatory lesions (**Figure 2B**) at week 12
  - By week 12, a significantly greater percent of subjects in the FCD105 group achieved IGA treatment success compared with the vehicle group
  - Daily application of FCD105 resulted in a significantly greater reduction in inflammatory lesions at week 12 compared with the vehicle group
- A numerical advantage of FCD105 vs. vehicle was observed in the absolute change in noninflammatory lesions at week 12 (**Figure 2C**)

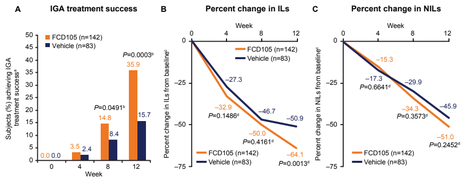
Figure 2. Co-primary efficacy endpoints at week 12 (ITT population with MI)



MI=multiple imputation.
[a]IGA treatment success is defined as an IGA score of 0 or 1, and at least a 2-grade improvement (decrease) from baseline.
[b]Cochran-Mantel-Haenszel test stratified by analysis center. *P*-value is for the null hypothesis that the risk ratio equals 1.
[c]Plotted data show the least squares means, which are defined as a model-based linear combination of the estimated effects.
[d]*P*-values are obtained from ANCOVA model with treatment as a main effect, baseline inflammatory lesion count as a covariate, and analysis center as a blocking factor.
[e]Mean baseline lesion counts.

- A significantly greater percent of subjects in the FCD105 group achieved IGA treatment success than those in the vehicle group as early as week 8 (**Figure 3A**)
- The time course of the percent change in inflammatory lesions from baseline demonstrated a numerical advantage of FCD105 over vehicle as early as week 4; this difference became significant at week 12 (**Figure 3B**)
- For the percent change in noninflammatory lesions, a numerical advantage of FCD105 over vehicle was observed by week 8 and maintained at week 12 (**Figure 3C**)

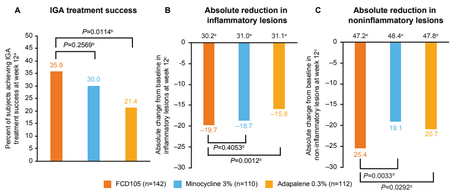
Figure 3. Efficacy of FCD105 throughout the study duration (ITT population with MI)



ILs-inflammatory lesions; NILs=non-inflammatory lesions.
[a]IGA treatment success is defined as an IGA score of 0 or 1, and at least a 2-grade improvement (decrease) from baseline.
[b]Cochran-Mantel-Haenszel test stratified by analysis center. *P*-value is for the null hypothesis that the risk ratio equals 1.
[c]Plotted data show the least squares means, which are defined as a model-based linear combination of the estimated effects.
[d]*P*-values are obtained from ANCOVA model with treatment as a main effect, baseline inflammatory lesion count as a covariate, and analysis center as a blocking factor.

- FCD105 achieved all secondary efficacy endpoints by demonstrating a numerical advantage over both individual components in the percent of subjects achieving IGA treatment success (**Figure 4A**) and the absolute reduction in noninflammatory lesions (**Figure 4C**) at week 12, as well as demonstrating a lack of numerical inferiority to either component in the absolute reduction in inflammatory lesions at week 12 (**Figure 4B**)
  - FCD105 showed statistically significant improvements compared with adapalene 0.3% in all three endpoints at week 12
  - There was a significantly greater reduction in noninflammatory lesions at week 12 in the FCD105 group compared with the minocycline 3% group

Figure 4. Secondary efficacy endpoints at week 12 (ITT population with MI)



MI=multiple imputation.
[a]IGA treatment success is defined as an IGA score of 0 or 1, and at least a 2-grade improvement (decrease) from baseline.
[b]Cochran-Mantel-Haenszel test stratified by analysis center. *P*-value is for the null hypothesis that the risk ratio equals 1.
[c]Plotted data show the least squares means, which are defined as a model-based linear combination of the estimated effects.
[d]*P*-values are obtained from ANCOVA model with treatment as a main effect, baseline inflammatory lesion count as a covariate, and analysis center as a blocking factor.
[e]Mean baseline lesion counts.

Safety Summary

- A summary of all AEs in the safety population is shown in **Table 2**
- There were no serious AEs reported during the course of the study
- Overall, most subjects reported AEs that were mild (10.3%) or moderate (4.0%) in severity
  - The incidence rate of severe AEs was similar across treatment groups
  - 2 subjects (0.4%) reported severe AEs
- A total of 4 subjects (0.9%) reported AEs that led to discontinuation of study drug

Table 2. Overall summary of adverse events (safety population)

	FCD105 (n=142)	Vehicle (n=82)	Minocycline 3% (n=110)	Adapalene 0.3% (n=112)	Overall (N=446)
Subjects with any AE, n (%)	21 (14.8)	10 (12.2)	15 (13.6)	20 (17.9)	66 (14.8)
Maximum severity, n (%)					
Mild	12 (8.5)	7 (8.5)	13 (11.8)	14 (12.5)	46 (10.3)
Moderate	9 (6.3)	3 (3.7)	2 (1.8)	4 (3.6)	18 (4.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)[a]	2 (0.4)
Subjects with any treatment-related AE, n (%)	5 (3.5)[b]	0 (0.0)	2 (1.8)[c]	10 (8.9)[d]	17 (3.8)
Subjects with any SAE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with any AE leading to discontinuation, n (%)	1 (0.7)[e]	0 (0.0)	0 (0.0)	3 (2.7)[f]	4 (0.9)
Subjects with any AE leading to death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AE=adverse event; TEAE=treatment-emergent adverse event; SAE=serious adverse event
[a]2 cases of acne.
[b]Dry skin, rash, dermatitis contact, pain of skin, burning sensation, and hypersesthesia.
[c]Dry skin and nail discoloration.
[d]4 cases of dry skin, 2 cases each of rash, acne, and eye irritation, and 1 case each of skin discoloration, skin irritation, and erythema of eyelid.
[e]Acne.
[f]2 cases of acne and 1 case of rash.

- The incidence rate of the most frequently reported TEAEs (≥2% in any group) was similar between treatment groups (**Table 3**)
- Three subjects withdrew from the study due to a treatment-related TEAE, all in the adapalene 0.3% group: acne, n=2 (1.8%); rash, n=1 (0.9%). There were no SAEs reported during the conduct of the study

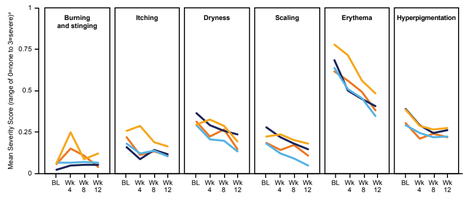
Table 3. Summary of TEAEs occurring in >2% of subjects in any treatment group (safety population)

System Organ Class/ Preferred Term, n (%)[a]	FCD105 (n=142)	Vehicle (n=82)	Minocycline 3% (n=110)	Adapalene 0.3% (n=112)	Overall (N=446)
Infections and infestations					
Upper respiratory tract infection	2 (1.4)	4 (4.9)	3 (2.7)	1 (0.9)	10 (2.2)
Nasopharyngitis	2 (1.4)	0 (0.0)	3 (2.7)	0 (0.0)	5 (1.1)
Viral upper respiratory tract infection	0 (0.0)	2 (2.4)	0 (0.0)	1 (0.9)	3 (0.7)
Skin and subcutaneous tissue disorders					
Dry skin	2 (1.4)	0 (0.0)	1 (0.9)	4 (3.6)	7 (1.6)
Nervous system disorders					
Headache	1 (0.7)	3 (3.7)	2 (1.8)	2 (1.8)	8 (1.8)

[a]Summary of TEAEs occurring in >2% of subjects in any treatment group, listed in descending order based on the overall total within each system organ class.

- Local facial tolerability assessments at week 12 demonstrated that FCD105 was well tolerated (**Figure 5**)
- The majority of subjects (≥89.9%) across all treatment groups recorded local tolerability assessments as "none" or "mild" at week 12; no notable differences were observed between treatment groups
- At least 93% of subjects treated with FCD105 rated local facial tolerability as "none" or "mild" for all 6 measures of local facial tolerability

Figure 5. Local facial tolerability assessments at week 12 (safety population, observed cases)



BL=baseline; Wk4=Week 4; Wk8=Week8; Wk12=Week 12.
[a]Local signs and symptoms were assessed on a 4-point scale including 0=none, 1=mild, 2=moderate, and 3=severe.

Summary

Limitations

- A limitation of the study relates to the generalizability of the data to a larger population or to patients less than 12 years of age
- Future studies are needed to confirm these findings and evaluate the safety profile of FCD105 over longer treatment durations

Conclusions

- Statistically significant improvement in disease burden was observed for FCD105 foam vs vehicle foam for the absolute change in inflammatory lesion count and IGA treatment success at week 12
- Numerical superiority was demonstrated for FCD105 over vehicle foam for the absolute change in noninflammatory lesions at week 12
- Numerical advantage of FCD105 foam over both minocycline 3% foam and adapalene 0.3% foam was observed at week 12, with the majority of comparisons being statistically significant
- TEAEs were few in type and frequency. Most were mild in severity, no serious TEAEs were reported, and subject discontinuations due to TEAEs were low
- FCD105 demonstrated a favorable tolerability profile, with most (≥93%) local signs and symptoms in this group being reported as "none" or "mild" at week 12
- These data are supportive to continue the development of FCD105 into Phase 3 clinical evaluation for the treatment of moderate-to-severe acne vulgaris

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Disclosures
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