Early Acne Improvements With Fixed-Combination Topical Therapy: Analysis of the First 4 Weeks of Treatment

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SYNOPSIS

- Acne treatment can take weeks to result in noticeable improvements, which may diminish patients' perception of effectiveness and negatively affect adherence[1]
- Therapies that deliver early visible improvements may encourage adherence, bolster overall treatment effectiveness, and minimize acne scarring[2,3]
- Combination topicals that target multiple acne pathophysiological pathways are more efficacious than monotherapies,[4] and simplified regimens using fixed combinations may improve adherence[2]
- Several fixed-combination topicals have been approved for acne, including various concentrations of adapalene (ADAP), benzoyl peroxide (BPO), clindamycin phosphate (CLIN), erythromycin (ERYTH), and/or tretinoin (TRET)[5]

OBJECTIVE

- To evaluate early acne improvements in clinical trials of fixed-combination acne topical treatments

METHODS

- Week 4 efficacy data for fixed-combination topicals were gathered from US Food and Drug Administration medical reviews, prescribing information, and/or publications of pivotal phase 2 and phase 3 trials
- For the only triple combination, data from a nonpivotal phase 2 study were also summarized, as that study included head-to-head comparisons to dyad combinations of the 3 active ingredients
- Analysis was limited to topicals for which week 4 data were reported for inflammatory lesion reductions (IL), noninflammatory lesion reductions (NIL), or treatment success (≥2-grade reduction in global acne severity score and clear/almost clear skin)
  - For acne lesions, mean percent changes from baseline were compiled; if unavailable, baseline counts and reductions at week 4 were used to calculate an estimated percent change from baseline

RESULTS

- Out of 12 fixed-combination topicals, data were available for 7, comprising combinations of ADAP (0.1-0.3%), BPO (2.5-5%), CLIN 1.2%, and TRET 0.1% (**Figure 1**)[6-21]
- Despite some differences in enrollment criteria, participant demographics and baseline characteristics were generally similar across studies
  - Minimum age for inclusion was 9-12 years, and mean ages in active treatment arms were 18-21 years
  - Across studies, most enrolled participants had moderate acne, though 1 study enrolled participants with mild acne (ADAP 0.1%/BPO 2.5% gel; Study SRE.18094), and 1 study enrolled equal percentages of participants with moderate and severe acne (ADAP 0.3%/BPO 2.5% gel)

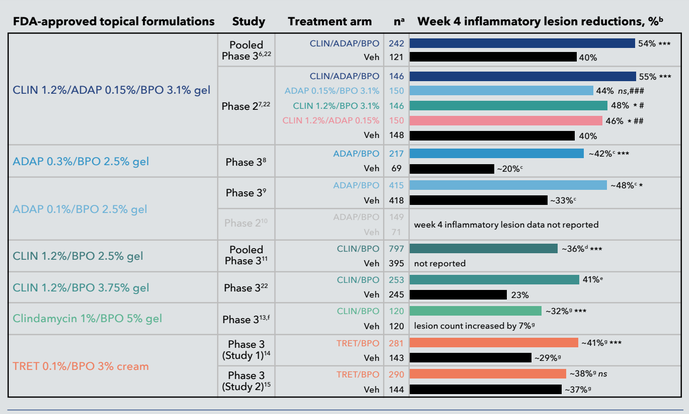
FIGURE 1. Fixed-Combination Topical Acne Treatments

Fixed-combination formulations	Clinical trial identifier or study name	
CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel Cabtreo® (Ortho Dermatologics)[6,7]	Phase 2: NCT03170388[a] Phase 3[b]: NCT04214639; NCT04214652	
ADAP 0.3%/BPO 2.5% gel Epiduo Forte® (Galderma)[8]	Phase 3: NCT01880320	
ADAP 0.1%/BPO 2.5% gel Epiduo® (Galderma)[9,10]	Phase 2: Study SRE.18094 Phase 3: NCT00422240(SRE.18087)	
CLIN 1.2%/BPO 2.5% gel Acanya® (Bausch Health)[11]	Phase 3[b]: Studies 012 and 017	
CLIN 1.2%/BPO 3.75% gel Onexton® (Bausch Health)[12]	Phase 3: Study V01-ACYC-301	
Clindamycin 1%/BPO 5% gel BenzaClin® (Valeant)[13]	Phase 3: Studies 1 and 2	
TRET 0.1%/BPO 3% cream Twyneo® (Galderma)[14]	Phase 3: Studies SGT-65-04 and SGT-65-05	
CLIN 1.2%/BPO 5% gel Duac® (Steifel)[15]	Studies 1/2/3/4/5	Not included in this analysis; week 4 efficacy data not reported
CLIN 1.2%/TRET 0.025% gel Veltin™ (Almirall)[16]	Study W0265-03	
CLIN 1.2%/TRET 0.025% gel Ziana™ (Bausch Health)[17,18]	Study 1: 7001.G2HP-06-02 Study 2: 7001.G2HP-07-02	
ERYTH 3%/BPO 5% gel Benzamycin® (Bausch Health)[19]	n/a	
ERYTH 3%/BPO 5% gel Aktipak® (Cutanea Life Sciences)[20,21]	Studies 1 and 2	

All treatments were applied once daily except for clindamycin 1%/BPO 5% gel, which was applied twice daily.
[a]This nonpivotal phase 2 study included dyad treatment arms: ADAP 0.15%/BPO3.1%, CLIN 1.2%/BPO 3.1%, and CLIN 1.2%/ADAP 0.15%, formulated in the same vehicle as the triple-combination product.
[b]This analysis includes data pooled from these studies.
[c]Clindamycin 1% is equivalent to CLIN 1.2%.
ADAP, adapalene; BPO, benzoyl peroxide; CLIN, clindamycin phosphate; ERYTH, erythromycin; n/a, efficacy data not available; TRET, tretinoin.

- At week 4, active treatments yielded IL reductions from baseline of 32-54%, whereas changes from baseline for vehicle ranged from an increase of 7% to a reduction of 40% (**Figure 2**)
  - In 7 of the 9 clinical trials that reported statistical comparisons, IL reductions with active treatment were significantly greater than with vehicle ($P<0.05$)
- Overall, greater IL reductions were observed with triple-combination CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel than with any of the dyad formulations, although statistical comparisons could not be made across clinical trials
- In the phase 2 study of CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel, IL reductions were significantly greater for the triple combination than for all dyad combinations of the 3 active ingredients ($P<0.05$)

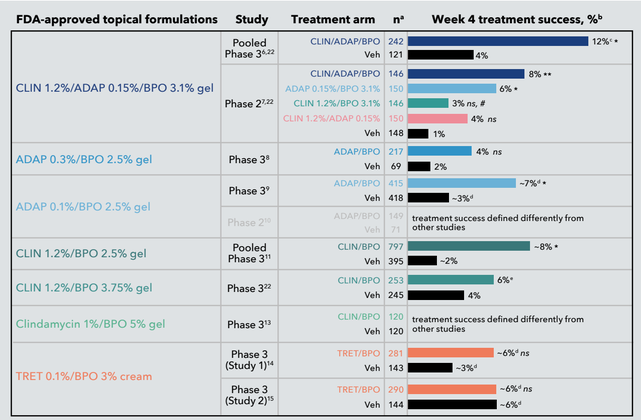
FIGURE 2. Inflammatory Lesion Reductions From Baseline at Week 4 With Fixed-Combination Topical Treatment



Intratrial comparisons: *$P<0.05$, ***$P\leq0.001$ vs vehicle. ns, not significant vs vehicle. #$P<0.05$, ##$P<0.01$, ###$P\leq0.001$ vs CLIN/ADAP/BPO.
Treatment arms for which week 4 data were not reported are indicated by gray text.
[a]Intent-to-treat populations.
[b]Mean or least-squares mean percent reductions from baseline are presented for all treatments except ADAP 0.1%/BPO 2.5%, for which median percent reductions are presented.
[c]Value was estimated from published figure.
[d]Population-level percent reduction in lesion count was calculated from mean absolute change at week 4 divided by mean count at baseline; *P*-value reflects absolute change.
[e]Statistical significance was not reported.
[f]In a second pivotal study,[23] absolute reduction from baseline to week 4 in inflammatory lesions was significantly greater for CLIN/BPO vs vehicle ($P\leq0.05$); however, the percent reduction could not be calculated because baseline count was not reported.
[g]Population-level percent reduction in lesion count was calculated from mean absolute change at week 4 (estimated from a figure) divided by mean count at baseline; *P*-values reflect absolute change.
ADAP, adapalene; BPO, benzoyl peroxide; CLIN, clindamycin phosphate; FDA, United States Food and Drug Administration; TRET, tretinoin; Veh, vehicle.

- The pattern of NIL reductions from baseline to week 4 was similar to that of IL, ranging from 25-45% with active treatment versus 19-32% with vehicle
  - In 8 of the 9 trials that reported statistical comparisons, NIL reductions were significantly greater with active treatment compared with vehicle ($P<0.05$)
- As with IL, NIL reductions were greater with triple-combination CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel (43% and 45%) than with any of the dyad formulations (25-38%)
- Rates of treatment success ranged from 3-12% with active treatments and 1-6% with vehicle (**Figure 3**)
- Treatment success rates with active treatments were significantly greater ($P<0.05$, all) than vehicle for triple-combination CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel (phase 2 and phase 3 studies) and ADAP 0.1%/BPO 2.5% gel (phase 3 study)

FIGURE 3. Treatment Success at Week 4 With Fixed-Combination Topical Treatment



Intra-trial comparisons: *$P<0.05$, **$P<0.01$ vs vehicle. ns, not significant vs vehicle.
Treatment arms for which week 4 data were not reported are indicated by gray text.
[a]Intent-to-treat populations.
[b]≥2-grade reduction in Evaluator's Global Severity Score and a score of 0 ("clear") or 1 ("almost clear").
[c]*P*-value from a logistic regression (using Firth's Penalized Likelihood) with factors of treatment group and analysis center. Values have been adjusted for multiple imputation using the Markov Chain Monte Carlo method.
[d]Value was estimated from published figure.
[e]Statistical significance was not reported.
ADAP, adapalene; BPO, benzoyl peroxide; CLIN, clindamycin phosphate; FDA, United States Food and Drug Administration; TRET, tretinoin; Veh, vehicle.

- For all studies that reported cutaneous safety/tolerability data for the first 4 weeks of treatment, events were[6-11,14]:
  - typical of topicals for acne (eg, scaling, burning, erythema)
  - transient, peaking within the first 2 weeks of treatment
  - mild overall in severity (mean scores <1 [mild] at all assessments)
- Limitations:
  - No head-to-head studies of branded topicals
  - Differences across studies in participants and methodology
  - Studies excluded due to differences in assessment criteria or data not reported

CONCLUSIONS

- In clinical trials of topical fixed-dose formulations for acne, triple-combination CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel yielded greater lesion reductions and rates of treatment success after 4 weeks of treatment than dyad formulations
- Even greater differences may be expected with real-world use, as early improvements may foster better long-term outcomes by increasing patients' confidence in and adherence to the treatment
- These week 4 findings are consistent with the greater 12-week clinical trial efficacy of CLIN 1.2%/ADAP 0.15%/BPO 3.1% gel versus other fixed-combination topical treatments[7]

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AUTHOR DISCLOSURES

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