Efficacy and Safety of Clindamycin Phosphate 1.2%/Adapalene 0.15%/Benzoyl Peroxide 3.1% Gel: Post Hoc Analysis by Baseline Disease Severity

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SYNOPSIS

- Acne can be difficult to treat because of its long treatment time course, chronicity, and poor patient adherence[1-3]
- Appropriate choice of acne therapy is influenced by several clinical features, including severity of disease[4]; therefore, it is important to determine the efficacy and safety of therapeutics in patients with varying degrees of baseline severity
- Clindamycin phosphate (CLIN) 1.2%/adapalene (ADAP) 0.15%/benzoyl peroxide (BPO) 3.1% gel (CAB) is the only FDA-approved triple-combination, fixed-dose topical for acne
- In 3 clinical studies of participants with moderate to severe acne, CAB showed superior efficacy versus component dyads and vehicle, with favorable safety and tolerability[5,6]

OBJECTIVE

- To assess efficacy and safety of CAB by baseline acne severity versus vehicle, 3 component dyads, and a branded ADAP/BPO

METHODS

- These post hoc analyses pooled data from two phase 2 (NCT03170388, NCT04892706) and two phase 3, double-blind, randomized 12-week studies (NCT04214639, NCT04214652)
- Eligible participants aged ≥9 years (≥12 years in NCT04892706) with moderate to severe acne were randomized to once-daily treatment with CAB or vehicle gel
  - One phase 2 study (NCT03170388) included treatment arms with 3 component dyad gels: ADAP/BPO, CLIN/BPO, and CLIN/ADAP
  - The other phase 2 study (NCT04892706) was a head-to-head comparison of CAB and a branded ADAP 0.3%/BPO 2.5% gel
- Efficacy assessments included least squares mean percent change from baseline in inflammatory/noninflammatory lesions and treatment success (≥2-grade reduction from baseline in Evaluator's Global Severity Score [EGSS] and clear/almost clear skin)
- Safety assessments included treatment-emergent adverse events (TEAEs) and cutaneous safety/tolerability
- Pooled participants were categorized by baseline disease severity: moderate (EGSS=3) or severe (EGSS=4)

RESULTS

Participants

- The pooled population comprised 1,787 participants, of which 1,557 (87%) had moderate acne and 230 (13%) had severe acne
- In those with moderate and severe acne, mean age ranged from 19.4–20.6 years and 17.3–19.9 years, respectively, across treatment groups
- The percentages of White and Black participants (self-reported race) were similar in those with moderate and severe acne (White, 72% and 73%; Black/African American, 15% and 12%, respectively)
- The percentage of females in the moderate group was higher than in the severe group (62% vs 47%)
- Demographics were generally similar across treatment groups

Efficacy

Lesion reductions

- After 12 weeks of CAB treatment, inflammatory and noninflammatory lesions were reduced >70% from baseline in participants with moderate and severe acne ($P<0.001$ vs vehicle; **Figure 1**)
- Moderate acne (at week 12):
  - Inflammatory lesion reductions were significantly greater with CAB than the 3 dyads ($P\leq0.001$, all) and the branded ADAP/BPO ($P<0.05$; **Figure 1A**)
  - Noninflammatory lesion reductions were numerically greater with CAB than all active treatments and significantly greater than the 3 dyads ($P<0.001$, all; **Figure 1B**)
- Severe acne (at week 12):
  - Inflammatory lesion reductions with CAB were significantly greater than 2 dyads (ADAP/BPO, CLIN/BPO; $P<0.05$) and similar to CLIN/ADAP and the branded ADAP/BPO (**Figure 1A**)
  - Noninflammatory lesion reductions were numerically greater with CAB than all active treatments and significantly greater than the ADAP/BPO dyad ($P<0.05$; **Figure 1B**)

Treatment success

- Moderate acne (at week 12): more than half of CAB-treated participants achieved treatment success, significantly greater than approximately one-fifth with vehicle and one-third treated with dyads or the branded ADAP/BPO ($P\leq0.001$, all; **Figure 2A**)
- Severe acne (at week 12): only CAB and CLIN/ADAP demonstrated significantly greater treatment success rates than vehicle in participants with severe acne ($P<0.05$; **Figure 2B**)

Safety/Tolerability

- Across all treatment groups, most TEAEs were of mild to moderate severity, and a low percentage of participants discontinued the studies owing to adverse events (**Table 1**)
  - Of all active treatments, the dyad ADAP/BPO had the highest rates of related TEAEs and discontinuations in participants with both moderate and severe acne; CLIN/BPO had the lowest rates of related TEAEs
- Mean cutaneous safety/tolerability scores at each postbaseline visit were ≤1 (1=mild) across severity groups (data not shown)

TABLE 1. Summary of Adverse Events Through Week 12 by Baseline Acne Severity (Safety Populations)

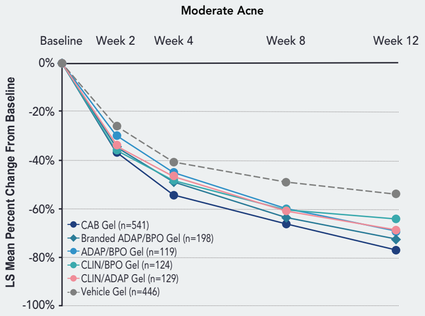
Moderate						
Participants, n (%)	CAB Gel (n=538)	Branded ADAP/BPO Gel (n=198)	ADAP/BPO Gel (n=117)	CLIN/BPO Gel (n=123)	CLIN/ADAP Gel (n=128)	Vehicle Gel (n=445)
TEAEs	170 (31.6)	69 (34.8)	40 (34.2)	22 (17.9)	37 (28.9)	62 (13.9)
Related	103 (19.1)	42 (21.2)	25 (21.4)	2 (1.6)	18 (14.1)	8 (1.8)
Discontinued drug or study due to AE	17 (3.2)	8 (4.0)	7 (6.0)	0	2 (1.6)	2 (0.4)
TEAE severity						
Mild	98 (18.2)	42 (21.2)	18 (15.4)	14 (11.4)	20 (15.6)	38 (8.5)
Moderate	63 (11.7)	25 (12.6)	18 (15.4)	8 (6.5)	15 (11.7)	22 (4.9)
Severe	9 (1.7)	2 (1.0)	4 (3.4)	0	2 (1.6)	2 (0.4)
Most common treatment-related TEAEs (≥2% participants in any treatment)						
AS pain	56 (10.4)	15 (7.6)	13 (11.1)	1 (0.8)	5 (3.9)	1 (0.2)
AS dryness	23 (4.3)	11 (5.6)	7 (6.0)	1 (0.8)	9 (7.0)	2 (0.4)
AS exfoliation	13 (2.4)	4 (2.0)	3 (2.6)	0	2 (1.6)	1 (0.2)
AS irritation	10 (1.9)	6 (3.0)	4 (3.4)	1 (0.8)	3 (2.3)	2 (0.4)
AS erythema	9 (1.7)	4 (2.0)	2 (1.7)	1 (0.8)	5 (3.9)	0
AS dermatitis	8 (1.5)	6 (3.0)	2 (1.7)	0	2 (1.6)	0

Severe						
Participants, n (%)	CAB Gel (n=75)	Branded ADAP/BPO Gel (n=28)	ADAP/BPO Gel (n=29)	CLIN/BPO Gel (n=21)	CLIN/ADAP Gel (n=20)	Vehicle Gel (n=50)
TEAEs	30 (40.0)	10 (35.7)	12 (41.4)	4 (19.0)	3 (15.0)	9 (18.0)
Related	12 (16.0)	2 (7.1)	7 (24.1)	1 (4.8)	0	1 (2.0)
Discontinued drug or study due to AE	0	0	2 (6.9)	0	1 (5.0)	0
TEAE severity						
Mild	11 (14.7)	7 (25.0)	7 (24.1)	2 (9.5)	0	3 (6.0)
Moderate	16 (21.3)	3 (10.7)	4 (13.8)	2 (9.5)	2 (10.0)	6 (12.0)
Severe	3 (4.0)	0	1 (3.4)	0	1 (5.0)	0
Most common treatment-related TEAEs (≥2% participants in any treatment)						
AS pain	8 (10.7)	1 (3.6)	3 (10.3)	0	0	1 (2.0)
AS dryness	2 (2.7)	0	1 (3.4)	1 (4.8)	0	0
AS rash	2 (2.7)	0	0	0	0	0
AS dermatitis	0	1 (3.6)	1 (3.4)	0	0	0
AS hypersensitivity	0	0	1 (3.4)	0	0	0
Erythema	2 (2.7)	0	0	0	0	0
Dermatitis contact	0	0	1 (3.4)	0	0	0

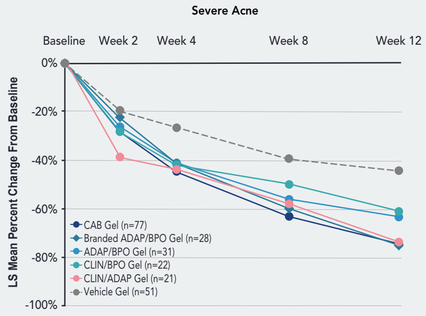
No serious adverse events in the studies were deemed related to treatment and all resolved.
Moderate acne=baseline EGSS 3; severe acne=baseline EGSS 4.
ADAP, adapalene; AE, adverse event; AS, application site; BPO, benzoyl peroxide; CAB, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%; CLIN, clindamycin phosphate; TEAE, treatment-emergent adverse event.

Figure 1. Reductions in Lesion Counts Through Week 12 by Baseline Acne Severity (ITT Population, Pooled Participants)

A. Inflammatory

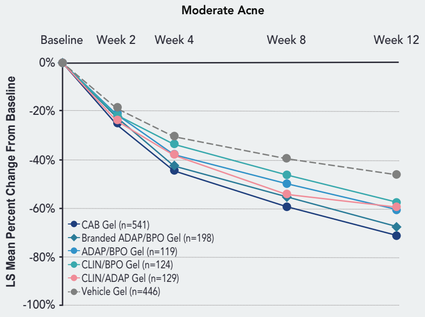


	CAB Gel (n=541)	Branded ADAP/BPO Gel (n=198)	ADAP/BPO Gel (n=119)	CLIN/BPO Gel (n=124)	CLIN/ADAP Gel (n=129)	Vehicle Gel (n=446)
Week 2	-37.3%***	-30.4%$^{\#\#}$	-30.9%$^{\#}$	-36.3%***	-34.9%**	-26.1%
Week 4	-54.9%***	-48.7%$^{***\#}$	-45.2%$^{\#\#}$	-48.5%$^{***\#}$	-46.8%$^{\#\#}$	-41.2%
Week 8	-66.1%***	-63.6%***	-60.2%$^{***\#}$	-61.0%***	-60.9%$^{***\#\#}$	-49.1%
Week 12	-77.1%***	-72.8%$^{***\#}$	-69.4%$^{***\#\#}$	-64.4%$^{***\#\#}$	-68.7%$^{***\#\#}$	-54.1%

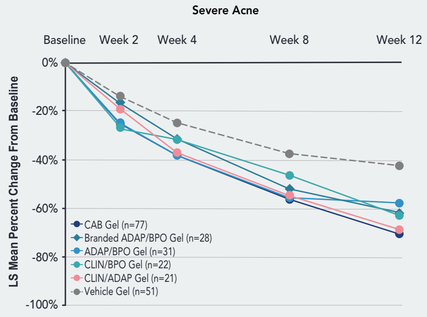


	CAB Gel (n=77)	Branded ADAP/BPO Gel (n=28)	ADAP/BPO Gel (n=31)	CLIN/BPO Gel (n=22)	CLIN/ADAP Gel (n=21)	Vehicle Gel (n=51)
Week 2	-29.0%*	-23.3%	-27.2%	-28.7%	-39.0%**	-19.8%
Week 4	-45.4%***	-42.0%*	-41.4%*	-41.9%*	-43.8%**	-26.4%
Week 8	-63.3%***	-60.1%**	-55.9%*	-49.9%$^{\#}$	-57.8%*	-39.3%
Week 12	-74.5%***	-75.4%***	-63.9%$^{*\#}$	-61.3%$^{\#}$	-73.7%***	-44.4%

B. Noninflammatory



	CAB Gel (n=541)	Branded ADAP/BPO Gel (n=198)	ADAP/BPO Gel (n=119)	CLIN/BPO Gel (n=124)	CLIN/ADAP Gel (n=129)	Vehicle Gel (n=446)
Week 2	-27.0%***	-24.1%	-22.1%	-22.8%	-25.9%$^{\#}$	-20.0%
Week 4	-45.0%***	-43.0%***	-38.3%$^{**\#}$	-33.9%$^{\#\#\#}$	-38.7%$^{**\#}$	-30.9%
Week 8	-59.7%***	-55.7%***	-50.3%$^{***\#\#}$	-47.0%$^{***\#\#}$	-54.4%$^{***\#}$	-40.1%
Week 12	-71.8%***	-68.2%***	-61.6%$^{***\#\#}$	-58.1%$^{***\#\#}$	-59.8%$^{***\#\#}$	-47.0%

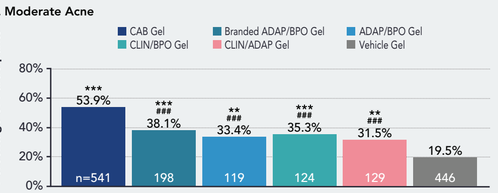


	CAB Gel (n=77)	Branded ADAP/BPO Gel (n=28)	ADAP/BPO Gel (n=31)	CLIN/BPO Gel (n=22)	CLIN/ADAP Gel (n=21)	Vehicle Gel (n=51)
Week 2	-20.0%	-17.6%	-26.2%	-28.0%*	-20.2%	-14.5%
Week 4	-39.7%**	-32.1%	-39.0%*	-32.2%	-37.6%	-25.2%
Week 8	-56.7%***	-52.8%	-56.4%**	-46.8%	-55.2%*	-37.6%
Week 12	-71.6%***	-62.7%*	-58.5%$^{\#}$	-64.1%**	-69.2%**	-43.1%

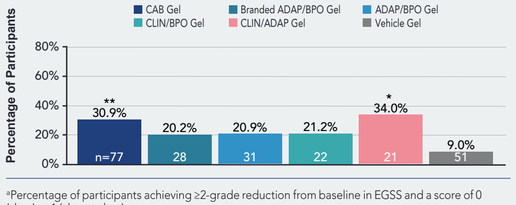
*P<0.05, **P<0.01, ***P≤0.001 vs vehicle; #P<0.05, ##P<0.01, ###P≤0.001 vs CAB gel.
Values have been adjusted for multiple imputation (MCMC).
Moderate acne=baseline EGSS 3; severe acne=baseline EGSS 4.
ADAP, adapalene; BPO, benzoyl peroxide; CAB, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%; CLIN, clindamycin phosphate; EGSS, Evaluator's Global Severity Score; LS, least squares; ITT, intent to treat; MCMC, Markov Chain Monte Carlo.

FIGURE 2. Treatment Success[a] at Week 12 by Baseline Acne Severity (ITT Populations)

A. Moderate Acne



B. Severe Acne



[a]Percentage of participants achieving ≥2-grade reduction from baseline in EGSS and a score of 0 (clear) or 1 (almost clear).
*P<0.05,**P<0.01, ***P≤ 0.001 vs vehicle; ###P≤ 0.001 vs CAB gel.
Values have been adjusted for multiple imputation (MCMC).
Moderate acne=baseline EGSS 3; severe acne=baseline EGSS 4.
ADAP, adapalene; BPO, benzoyl peroxide; CAB, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%; CLIN, clindamycin phosphate; EGSS, Evaluator's Global Severity Score; ITT, intent to treat; MCMC, Markov Chain Monte Carlo.

CONCLUSIONS

- Degree of acne severity is a key clinical feature used to determine appropriate choice of treatment
- In 4 clinical trials, CAB gel—the only fixed-dose, triple-combination topical treatment approved for acne—consistently demonstrated efficacy, safety, and tolerability in participants with either moderate or severe acne
- CAB gel demonstrated superior efficacy compared with its 3 component dyads and branded ADAP/BPO in participants with moderate acne and generally numerically greater efficacy than dyads and branded ADAP/BPO in participants with severe acne
  - A limitation to these post hoc analyses is the small population of participants in the severe acne group
- Owing to the multifactorial pathogenesis of acne, a triple-combination topical treatment may result in clinical success more often than monotherapy or dyad combination products
- To our knowledge, these analyses of combination topical acne treatments include data from the only double-blind, vehicle-controlled head-to-head study

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AUTHOR DISCLOSURES

Michael Gold has acted as an investigator, advisor, speaker, and consultant for Ortho Dermatologics. Edward (Ted) Lain has served as investigator, consultant, and/or speaker for Ortho Dermatologics, AbbVie, Almirall, Amgen, Arcutis, Dermavant, EPI Health, Galderma, Incyte, LEO Pharma, Novartis, Eli Lilly, Pfizer, Sun Pharma, UCB, Endo International, ChemoCentryx, Biorasi, Sirnaomics, Evelo Biosciences, Concert Pharmaceuticals, Cara Therapeutics, Castle Biosciences, Mindera, Biofrontera, Alfasigma, AiViva Biopharma, Anaptys Bio, Bausch Health, Dr Reddy's, and Trevi Therapeutics. Julie C. Harper has received honoraria from Almirall, Galderma, LaRoche-Posay, Ortho Dermatologics, and Sun Pharma. Hilary Baldwin has served as advisor, investigator, and on speakers bureaus for Almirall, Cassiopea, Foamix, Galderma, Ortho Dermatologics, Sol Gel, and Sun Pharma. Linda Stein Gold has served as investigator/consultant or speaker for Ortho Dermatologics, LEO Pharma, Dermavant, Incyte, Novartis, AbbVie, Pfizer, Sun Pharma, UCB, Arcutis, and Lilly. Eric Guenin is an employee of Ortho Dermatologics and may hold stock and/or stock options in its parent company.

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