The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

GSK Medicine: Clindamycin 1%-Benzoyl peroxide 3% gel

Study Number: 201884

Title: Clinical evaluation of efficacy at 2 weeks of Duac® fixed dose combination gel in treatment of facial acne vulgaris in Japanese Subjects.

Rationale: This study was planned to compare the efficacy and safety of Clindamycin 1%-Benzoyl peroxide 3% gel (CLDM 1%/BPO 3%), once daily for 12 weeks in Japanese subjects with acne vulgaris to the combination therapy of adapalene (ADA) 0.1% and CLDM 1% (ADA + CLDM), which is recommended as a standard therapy in Japanese Acne Treatment Guidelines.

Phase: IV

Study Period: 7 October 2015 - 17 February 2016

Study Design: This was a multicenter, randomized, active-controlled, single-blind (investigator-blinded), parallel-group study. The study was conducted over a 12-week treatment period with visits at screening (baseline [Week 0/Day 1]) and Weeks 1, 2, 4, 8, and 12 (or the end of study).

Centres: 15 centres in Japan

Indication: Acne vulgaris

Treatment: The subjects were randomized (1:1) at baseline to receive CLDM 1%/BPO 3% once daily or the combination therapy of ADA 0.1% once daily and CLDM 1% twice daily for 12 weeks, with instructions to apply a sufficient amount of the investigational product to cover the entire face (CLDM 1%/BPO 3%, ADA) or inflammatory lesions (CLDM). CLDM was not permitted to be applied to subjects without inflammatory lesions (ILs).

Objectives: To compare the early efficacy of CLDM 1%/BPO 3% once daily to the combination therapy of ADA once daily and CLDM twice daily at Week 2.

Primary Outcome (Endpoints)/Efficacy: The percent change in total lesion counts (TLs) from baseline to Week 2.

Secondary Outcome (Endpoints)/Efficacy:

- The percent change in TLs from baseline to Weeks 1, 4, 8, and 12 (or the end of study).
- The percent change in lesion counts (ILs and non-inflammatory lesion counts [non-ILs]) from baseline to Weeks 1, 2, 4, 8, and 12 (or the end of study).
- The absolute change in lesion counts (TLs, ILs and non-ILs) from baseline to Weeks 1, 2, 4, 8, and 12 (or the end of study).
- The proportion of subjects who have a minimum 2-grade improvement in Investigator's Static Global Assessment (ISGA) score from baseline to Weeks 1, 2, 4, 8, and 12 (or the end of study).
- The proportion of subjects who have an ISGA score of 0 or 1 at Weeks 1, 2, 4, 8, and 12 (or the end of study).
- The proportion of subjects who have a reduction in lesion counts (TLs, ILs and non-ILs) of at least 50% from baseline to Weeks 1, 2, 4, 8, and 12 (the end of study).

Statistical Methods:

<Sample Size Considerations>

The sample size in this study was planned to be a total of 350 subjects (CLDM 1%/BPO 3% group: 175; ADA + CLDM group: 175). Based on a previous Japanese phase III study (Study ID: STF115287) and scientific literature, the mean percent reductions from baseline in TLs at Week 2 were estimated as 45% and 35% for the CLDM 1%/BPO 3% group and the ADA + CLDM group, respectively. Assuming a 28% common standard deviation (SD) and a two-sided significance level of 5%, 175 subjects per application group provided approximately a 90% power to detect a 10% treatment difference between CLDM 1%/BPO 3% and ADA + CLDM using a two sample t-test. And the minimum detectable effect was approximately 6% when 175 subjects per group and a 28% common SD were assumed with a two-sided significance level of 5%.

<Analysis Populations>

- ITT (Intent-To-Treat) population

This population was defined as all randomized subjects who received at least one application of study product. The ITT population was used for efficacy and safety analyses.

<Efficacy Analyses>

· Primary Analysis

The primary endpoint in this study was the percent change from baseline in TLs at Week 2. The percent change from baseline in TLs was analyzed using a mixed model for repeated measures (MMRM). The MMRM model included the fixed, categorical effects of treatment, center, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline TLs and baseline value-by-visit interaction. An unstructured variance structure was used to model the within-subject errors, shared across treatments. The model was fitted using the MIXED procedure in SAS, with the Kenward-Roger option to estimate denominator degrees of freedom and standard errors (SEs). The adjusted means (least square means) and corresponding SEs of means were estimated for each treatment by visit, together with estimated treatment differences, corresponding 95% confidence interval (CI) and p-values. The primary treatment comparison was the contrast between treatments at Week 2. The treatment difference was tested at a two-sided significance level of 5%.

· Secondary Analyses

The following endpoints were also analyzed using the MMRM as well as the primary analysis. The treatment comparison at each visit was conducted based on adjusted means at a significance level of 5% and the treatment difference was estimated with the 95% CI based on the model.

- ✧ The percent change from baseline in lesion counts (TLs [excluding Week 2], ILs, and non-ILs)
- ✧ The absolute change from baseline in lesion counts (TLs, ILs, and non-ILs)

The following endpoints were analyzed using the Cochran-Mantel-Haenszel test stratified by center. The treatment comparison was conducted at a two-sided significance level of 5%.

- ✧ The proportion of subjects with a minimum 2-grade improvement in ISGA score from baseline
- ✧ The proportion of subjects who had an ISGA score of 0 or 1
- ✧ The proportion of subjects with at least a 50% reduction in lesion counts (TLs, ILs, and non-ILs)

No multiplicity adjustment was made to secondary objectives.

<Safety Analyses>

All Adverse events (AEs) that occurred during the study were recorded and classified using the Medical Dictionary for Regulatory Activities (Version 18.1). Frequencies of AEs and percentages of subjects reporting them were presented overall, as well as by system organ class and preferred term.

Skin tolerability assessments of erythema, dryness, peeling, itching, and burning/stinging were presented as frequency tabulations for the number and percentage of subjects in each category by treatment group. Summary statistic of observed values and absolute changes from baseline at each visit were analyzed by treatment. Summaries of all local tolerability assessments were provided.

Study Population: Eligible subjects included males and females, 12 to 45 years (inclusive) of age. At screening (baseline [Week 0/Day 1]), subjects had a minimum of 17 and not more than 60 ILs (papules plus pustules, including nasal lesions) and a minimum of 20 and not more than 150 non-ILs (open and closed comedones, including nasal lesions) confined to the facial area, as well as an ISGA score of 2 or greater.

	CLDM 1%/BPO 3%	**ADA + CLDM**
Number of Subjects:		
Planned, N	175	175
Randomised, N	174	177
Completed, n (%)	165 (96)	169 (95)
Total Number Subjects Withdrawn, n (%)	7 (4)	8 (5)
Withdrawn due to Adverse Events, n (%)	6 (3)	5 (3)
Withdrawn for other reasons, n (%)	1 (<1)	3 (2)
Demographics	**CLDM 1%/BPO 3%**	**ADA + CLDM**
N (ITT)	172	177
Females: Males	97: 75	110: 67
Mean Age, years (SD)	20.3 (5.91)	19.8 (4.90)
Asian - Japanese Heritage, n (%)	172 (100)	177 (100)

Primary Efficacy Results: **The percent change in TLs from baseline to Week 2 (ITT, MMRM)**			
		CLDM 1%/BPO 3% (N=172)	**ADA + CLDM (N=177)**
Adjusted Mean (SE)		-42.16 (1.890)	-35.33 (1.850)
Difference versus (vs) ADA + CLDM		-6.83	
95% CI		-11.88, -1.78	
p-value		0.008	
Secondary Outcome Results:			
The percent change in TLs from baseline to Weeks 1, 4, 8, and 12 (ITT, MMRM)			
Week 1	n	172	176
	Adjusted Mean (SE)	-24.58 (1.729)	-24.33 (1.697)
	Difference vs ADA + CLDM	-0.25	
	95% CI	-4.85, 4.35	
Week 4	n	169	174
	Adjusted Mean (SE)	-55.51 (1.670)	-49.65 (1.637)
	Difference vs ADA + CLDM	-5.85	
	95% CI	-10.29, -1.42	
Week 8	n	167	172
	Adjusted Mean (SE)	-65.23 (1.544)	-62.88 (1.514)
	Difference vs ADA + CLDM	-2.35	
	95% CI	-6.42, 1.72	
Week 12	n	164	169
	Adjusted Mean (SE)	-74.60 (1.314)	-71.36 (1.288)
	Difference vs ADA + CLDM	-3.24	
	95% CI	-6.64, 0.16	
The percent change in ILs from baseline to Weeks 1, 2, 4, 8, and 12 (ITT, MMRM)			
Week 1	n	172	176
	Adjusted Mean (SE)	-42.97 (2.349)	-37.89 (2.309)
	Difference vs ADA + CLDM	-5.08	
	95% CI	-11.41, 1.25	
Week 2	n	169	176
	Adjusted Mean (SE)	-60.92 (2.209)	-52.49 (2.162)
	Difference vs ADA + CLDM	-8.43	
	95% CI	-14.35, -2.51	
Week 4	n	169	174
	Adjusted Mean (SE)	-70.68 (1.898)	-61.30 (1.860)
	Difference vs ADA + CLDM	-9.37	
	95% CI	-14.42, -4.33	
Week 8	n	167	172
	Adjusted Mean (SE)	-76.33 (1.717)	-69.64 (1.682)
	Difference vs ADA + CLDM	-6.69	
	95% CI	-11.21, -2.16	
Week 12	n	164	169
	Adjusted Mean (SE)	-82.07 (1.403)	-77.58 (1.374)
	Difference vs ADA + CLDM	-4.50	
	95% CI	-8.10, -0.89	
The percent change in non-ILs from baseline to Weeks 1, 2, 4, 8, and 12 (ITT, MMRM)			
Week 1	n	172	176
	Adjusted Mean (SE)	-15.13 (2.279)	-17.85 (2.239)
	Difference vs ADA + CLDM	2.71	
	95% CI	-3.38, 8.80	

Week 2	n	169	176
	Adjusted Mean (SE)	-32.71 (2.419)	-27.01 (2.367)
	Difference vs ADA + CLDM	-5.69	
	95% CI	-12.17, 0.78	
Week 4	n	169	174
	Adjusted Mean (SE)	-47.64 (2.171)	-43.74 (2.129)
	Difference vs ADA + CLDM	-3.89	
	95% CI	-9.67, 1.88	
Week 8	n	167	172
	Adjusted Mean (SE)	-59.50 (1.910)	-58.91 (1.872)
	Difference vs ADA + CLDM	-0.59	
	95% CI	-5.61, 4.44	
Week 12	n	164	169
	Adjusted Mean (SE)	-71.07 (1.603)	-67.29 (1.571)
	Difference vs ADA + CLDM	-3.78	
	95% CI	-7.92, 0.35	
The absolute change in TLs from baseline to Weeks 1, 2, 4, 8, and 12 (ITT)			
Screening (baseline)	n	172	177
	Mean (SD)	102.7 (35.67)	101.9 (36.55)
Change from baseline			
Week 1	n	172	176
	Mean (SD)	-28.5 (25.64)	-28.0 (23.30)
Week 2	n	169	176
	Mean (SD)	-45.9 (27.08)	-39.3 (31.61)
Week 4	n	169	174
	Mean (SD)	-60.4 (31.52)	-54.7 (33.25)
Week 8	n	167	172
	Mean (SD)	-70.7 (33.88)	-68.8 (34.87)
Week 12	n	164	169
	Mean (SD)	-80.7 (34.03)	-78.1 (36.33)
The absolute change in ILs from baseline to Weeks 1, 2, 4, 8, and 12 (ITT)			
Screening (baseline)	n	172	177
	Mean (SD)	32.4 (11.84)	31.8 (12.47)
Change from baseline			
Week 1	n	172	176
	Mean (SD)	-14.4 (11.12)	-12.4 (10.31)
Week 2	n	169	176
	Mean (SD)	-20.5 (11.20)	-17.3 (11.27)
Week 4	n	169	174
	Mean (SD)	-23.7 (10.85)	-20.5 (11.90)
Week 8	n	167	172
	Mean (SD)	-25.5 (11.11)	-23.1 (12.08)
Week 12	n	164	169
	Mean (SD)	-27.2 (11.02)	-25.6 (11.71)
The absolute change in non-ILs from baseline to Weeks 1, 2, 4, 8, and 12 (ITT)			
Screening (baseline)	n	172	177
	Mean (SD)	70.4 (30.99)	70.1 (31.84)
Change from baseline			
Week 1	n	172	176
	Mean (SD)	-14.1 (20.35)	-15.5 (19.73)
Week 2	n	169	176
	Mean (SD)	-25.4 (22.18)	-22.0 (25.86)
Week 4	n	169	174
	Mean (SD)	-36.8 (26.99)	-34.2 (26.91)

Week 8	n	167	172
	Mean (SD)	-45.2 (28.43)	-45.7 (29.19)
Week 12	n	164	169
	Mean (SD)	-53.5 (28.40)	-52.5 (31.46)
The proportion of subjects who have a minimum 2-grade improvement in ISGA score from baseline to Weeks 1, 2, 4, 8, and 12 (ITT)			
Week 1	Responder / n, (%)	4 / 172 (2)	0 /177
Week 2	Responder / n, (%)	10 / 172 (6)	5 / 177 (3)
Week 4	Responder / n, (%)	20 / 172 (12)	14 / 177 (8)
Week 8	Responder / n, (%)	38 / 172 (22)	21 / 177 (12)
Week 12	Responder / n, (%)	64 / 172 (37)	47 / 177 (27)
The proportion of subjects who have an ISGA score of 0 or 1 at Weeks 1, 2, 4, 8, and 12 (ITT)			
Week 1	Responder / n, (%)	4 / 172 (2)	1 / 177 (<1)
Week 2	Responder / n, (%)	10 / 172 (6)	8 / 177 (5)
Week 4	Responder / n, (%)	22 / 172 (13)	10 / 177 (6)
Week 8	Responder / n, (%)	34 / 172 (20)	21 / 177 (12)
Week 12	Responder / n, (%)	70 / 172 (41)	52 / 177 (29)
The proportion of subjects who have a reduction in TLs of at least 50% from baseline to Weeks 1, 2, 4, 8, and 12 (ITT)			
Week 1	Responder / n, (%)	38 / 172 (22)	32 / 176 (18)
Week 2	Responder / n, (%)	81 / 172 (47)	75 / 177 (42)
Week 4	Responder / n, (%)	116 / 172 (67)	107 / 177 (60)
Week 8	Responder / n, (%)	139 / 172 (81)	144 / 177 (81)
Week 12	Responder / n, (%)	151 / 172 (88)	152 / 177 (86)
The proportion of subjects who have a reduction in ILs of at least 50% from baseline to Weeks 1, 2, 4, 8, and 12 (ITT)			
Week 1	Responder / n, (%)	88 / 172 (51)	74 / 176 (42)
Week 2	Responder / n, (%)	132 / 172 (77)	116 / 177 (66)
Week 4	Responder / n, (%)	146 / 172 (85)	135 / 177 (76)
Week 8	Responder / n, (%)	150 / 172 (87)	148 / 177 (84)
Week 12	Responder / n, (%)	158 / 172 (92)	158 / 177 (89)
The proportion of subjects who have a reduction in non-ILs of at least 50% from baseline to Weeks 1, 2, 4, 8, and 12 (ITT)			
Week 1	Responder / n, (%)	24 / 172 (14)	28 / 176 (16)
Week 2	Responder / n, (%)	64 / 172 (37)	60 / 177 (34)
Week 4	Responder / n, (%)	100 / 172 (58)	96 / 177 (54)
Week 8	Responder / n, (%)	125 / 172 (73)	130 / 177 (73)
Week 12	Responder / n, (%)	142 / 172 (83)	142 / 177 (80)
Safety Results: On-therapy AEs including serious adverse events (SAEs) were collected from the start of study treatment until Week 12 or premature withdrawal.			
Most Frequent Adverse Events – On-Therapy (the most frequent 10 events in each group)			
		CLDM 1%/BPO 3% (N=172)	**ADA + CLDM (N=177)**
Subjects with any AE(s), n (%)		53 (31)	100 (56)
Application site dryness		16 (9)	44 (25)
Nasopharyngitis		12 (7)	15 (8)
Application site pain		3 (2)	20 (11)
Application site erythema		4 (2)	11 (6)
Application site pruritus		5 (3)	8 (5)
Eczema		2 (1)	10 (6)
Application site exfoliation		3 (2)	6 (3)
Application site reaction		2 (1)	5 (3)
Urticaria		2 (1)	2 (1)
Application site dermatitis		0	3 (2)
Dermatitis contact		0	3 (2)

Sinusitis		2 (1)	0
Serious Adverse Events - On-Therapy **n (%) [n considered by the investigator to be related to study medication]**			
		CLDM 1%/BPO 3% (N=172)	**ADA + CLDM (N=177)**
Subjects with non-fatal SAEs, n (%) [related]		1 (<1) [0]	0
Duodenal ulcer [related]		1 (<1) [0]	0
Subjects with fatal SAEs, n (%) [related]		0	0
Local tolerability scores over all study time points (ITT)			
		CLDM 1%/BPO 3% (N=172)	**ADA + CLDM (N=177)**
Erythema			
Screening (baseline)	n	172	177
	Mean (SD)	0.4 (0.79)	0.5 (0.83)
Week 1	n	170	175
	Mean (SD)	0.4 (0.79)	0.8 (0.96)
Week 2	n	169	175
	Mean (SD)	0.4 (0.77)	0.5 (0.84)
Week 4	n	169	174
	Mean (SD)	0.3 (0.61)	0.3 (0.66)
Week 8	n	165	171
	Mean (SD)	0.2 (0.53)	0.3 (0.63)
Week 12	n	165	168
	Mean (SD)	0.2 (0.55)	0.2 (0.43)
Withdrawal	n	7	7
	Mean (SD)	1.6 (1.40)	1.6 (1.27)
Dryness			
Screening (baseline)	n	172	177
	Mean (SD)	0.1 (0.34)	0.1 (0.27)
Week 1	n	170	175
	Mean (SD)	0.2 (0.54)	0.7 (0.93)
Week 2	n	169	175
	Mean (SD)	0.1 (0.46)	0.2 (0.53)
Week 4	n	169	174
	Mean (SD)	0.1 (0.43)	0.1 (0.45)
Week 8	n	165	171
	Mean (SD)	0.1 (0.52)	0.1 (0.42)
Week 12	n	165	168
	Mean (SD)	0.1 (0.36)	0.1 (0.34)
Withdrawal	n	7	7
	Mean (SD)	1.1 (1.57)	0.9 (1.21)
Peeling			
Screening (baseline)	n	172	177
	Mean (SD)	0.0 (0.11)	0.0 (0.18)
Week 1	n	170	175
	Mean (SD)	0.1 (0.42)	0.5 (0.89)
Week 2	n	169	175
	Mean (SD)	0.1 (0.31)	0.2 (0.51)
Week 4	n	169	174
	Mean (SD)	0.1 (0.32)	0.1 (0.37)
Week 8	n	165	171
	Mean (SD)	0.1 (0.38)	0.1 (0.42)
Week 12	n	165	168
	Mean (SD)	0.0 (0.31)	0.1 (0.27)
Withdrawal	n	7	7

	Mean (SD)	0.7 (1.11)	0.7 (1.25)
Itching			
Screening (baseline)	n	172	177
	Mean (SD)	0.3 (0.57)	0.3 (0.55)
Week 1	n	170	175
	Mean (SD)	0.2 (0.58)	0.4 (0.72)
Week 2	n	169	175
	Mean (SD)	0.2 (0.57)	0.4 (0.67)
Week 4	n	169	174
	Mean (SD)	0.2 (0.52)	0.2 (0.40)
Week 8	n	165	171
	Mean (SD)	0.1 (0.31)	0.1 (0.37)
Week 12	n	165	168
	Mean (SD)	0.1 (0.36)	0.1 (0.26)
Withdrawal	n	7	7
	Mean (SD)	0.7 (1.25)	1.0 (0.82)
Burning/Stinging			
Screening (baseline)	n	172	177
	Mean (SD)	0.1 (0.37)	0.1 (0.35)
Week 1	n	170	175
	Mean (SD)	0.1 (0.36)	0.6 (0.84)
Week 2	n	169	175
	Mean (SD)	0.1 (0.46)	0.3 (0.60)
Week 4	n	169	174
	Mean (SD)	0.1 (0.33)	0.1 (0.36)
Week 8	n	165	171
	Mean (SD)	0.1 (0.28)	0.1 (0.47)
Week 12	n	165	168
	Mean (SD)	0.1 (0.33)	0.1 (0.25)
Withdrawal	n	7	7
	Mean (SD)	0.3 (0.76)	1.1 (1.21)

Conclusion:
There was a statistically significant difference between the CLDM 1%/BPO 3% group and the ADA + CLDM group for the adjusted mean percent change from baseline at Week 2 in TLs (-6.83 [95% CI: -11.88, -1.78], p=0.008).

In the CLDM 1%/BPO 3% group, 53 subjects reported non-serious AEs with the most frequently reported being application site dryness, nasopharyngitis, and application site pruritus. In the ADA + CLDM group, 100 subjects reported non-serious AEs with the most frequently reported being application site dryness, application site pain, and nasopharyngitis. One non-fatal SAE; duodenal ulcer was reported in one subject in the CLDM 1%/BPO 3% group during the study treatment period. There were no fatal SAEs reported in this study.