Report on the Deliberation Results

January 26, 2015
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

[Brand name]	Duac Combination Gel
[Non-proprietary name]	Clindamycin Phosphate Hydrate/Benzoyl Peroxide (JAN*)
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	March 24, 2014

[Results of deliberation]
In the meeting held on January 21, 2015, the Second Committee on New Drugs concluded that the product may be approved and that its result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The reexamination period should be the remaining of the reexamination period (until December 25, 2022) for Bepio Gel 2.5%, which contains benzoyl peroxide, an active ingredient of the drug product, which is not classified as a poisonous drug, a powerful drug, a biological product, or a specified biological product.

[Conditions for approval]
The applicant is required to develop and appropriately implement a risk management plan.

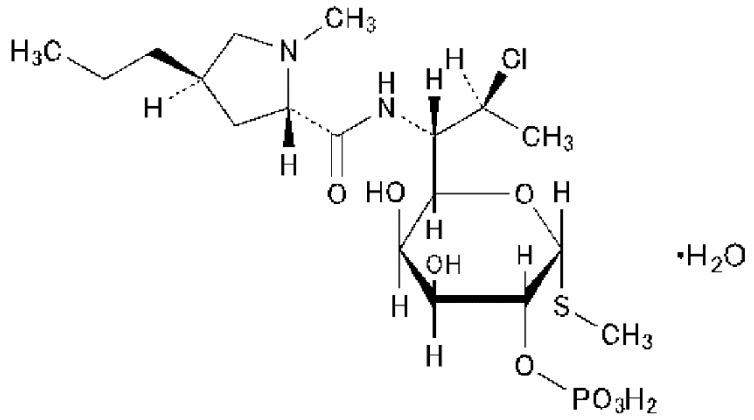
**Japanese Accepted Name (modified INN)*

Review Report

January 8, 2015
Pharmaceuticals and Medical Devices Agency

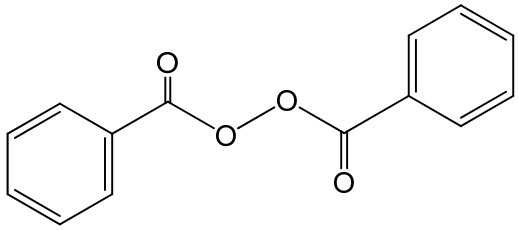
The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Duac Combination Gel
[Non-proprietary name]	Clindamycin Phosphate Hydrate/Benzoyl Peroxide
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	March 24, 2014
[Dosage form/Strength]	Combination gel containing 10 mg clindamycin, as phosphate hydrate, and 30 mg benzoyl peroxide per gram.
[Application classification]	Prescription drug (1) Drug containing a new active ingredient (benzoyl peroxide), and (2) new prescription combination drug
[Chemical structure]	Clindamycin Phosphate Hydrate



Molecular formula: $C_{18}H_{34}ClN_2O_8PS \cdot H_2O$
Molecular weight: 522.98
Chemical name: Methyl 7-chloro-6,7,8-trideoxy-6-[(2*S*,4*R*)-1-methyl-4-propylpyrrolidine-2-carboxamido]-1-thio-L-*threo*-α-D-*galacto*-octopyranoside 2-(dihydrogen phosphate)monohydrate

Benzoyl Peroxide



Molecular formula: $C_{14}H_{10}O_4$

Molecular weight: 242.23

Chemical name: Dibenzoyl peroxide

[Items warranting special mention] None

[Reviewing office] Office of New Drug IV

Review Results

January 8, 2015

[Brand name]	Duac Combination Gel
[Non-proprietary name]	Clindamycin Phosphate Hydrate/Benzoyl Peroxide
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	March 24, 2014

[Results of review]

Based on the submitted data, it is concluded that the efficacy of the product in patients with acne vulgaris has been demonstrated, and its safety is acceptable in view of its observed benefits.

As a result of its regulatory review, PMDA concluded that this product may be approved for the following indication and dosage and administration, with the following conditions for approval.

[Indications]	Applicable microorganisms *Staphylococcus* spp. and *Propionibacterium acnes* susceptible to Clindamycin Phosphate Hydrate/Benzoyl Peroxide Indication Acne vulgaris
[Dosage and administration]	An appropriate amount of Clindamycin Phosphate Hydrate/Benzoyl Peroxide Gel, 1%/3%, should be applied once daily to the affected areas on the face after washing.
[Conditions for approval]	The applicant is required to develop and appropriately implement a risk management plan.

Review Report (1)

November 4, 2014

I. Product Submitted for Registration

[Brand name]	Duac Combination Gel
[Non-proprietary name]	Clindamycin Phosphate Hydrate/Benzoyl Peroxide (JAN*)
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	March 24, 2014
[Dosage form/Strength]	Combination gel containing 10 mg clindamycin, as phosphate hydrate, and 30 mg benzoyl peroxide per gram
[Proposed indications]	Applicable microorganisms *Staphylococcus* spp. and *Propionibacterium acnes* susceptible to Clindamycin Phosphate Hydrate Benzoyl Peroxide Indication Acne vulgaris
[Proposed dosage and administration]	An appropriate amount of Clindamycin Phosphate Hydrate/Benzoyl Peroxide Gel, 1%/3%, should be applied once daily to the affected areas on the face after washing.

II. Summary of the Submitted Data and Outline of Review by the Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

1. Origin or history of discovery, use in foreign countries, and other information

Clindamycin phosphate (CLDM) hydrate equivalent to 1% clindamycin and 3% benzoyl peroxide (BPO) are contained as active ingredients in Duac Combination Gel (hereinafter also referred to as CLDM/BPO Gel, 1%/3%), a gel for external use. In Japan, topical products containing 1% CLDM, a lincomycin antibiotic, was approved in 2002 for the treatment of acne (with suppurative inflammation).[1)] BPO is a bactericidal antimicrobial agent that has a keratolytic action, and topical products containing BPO as a single active ingredient have been used for the treatment of acne vulgaris outside Japan.[2),3)] However, as of October 2014, no topical products containing BPO are approved in Japan.

[1)] In a notice of the results of reevaluation of antimicrobial agents (PFSB Notification No. 0930006, dated September 30, 2004), acne vulgaris (with multiple inflammatory papules) was replaced with "acne (with suppurative inflammation)."

[2)] Pace WE, *Canad Med Ass J.*1965;93:252-254

[3)] These products are available as over-the-counter (OTC) drugs or other products in various forms such as gels, lotions, creams, toners, and soaps, and they contain BPO at a concentration ranging from 2.5 to 20%.

Acne vulgaris is a skin disease with eruptions, often occurring on the face, upper back, and chest during or after puberty,[4),5)] and classified mainly into non-inflammatory lesions (open and closed comedones), and inflammatory lesions (red papules, pustules, cysts, and nodules). This condition is caused by abnormal lipid metabolism, hornification disorder, or overgrowth of skin flora.

The Guidelines for the Treatment of Acne Vulgaris available in Japan[6)] recommend topical use of adapalene or oral or topical use of antimicrobial agents in monotherapy or combination therapy according to the severity of comedones, papules, or cysts. Guidelines published outside Japan recommend topical antimicrobial agents and BPO in combination,[7)] or gels containing CLDM and BPO,[8)] in addition to the drugs recommended in Japan.

A topical gel containing CLDM and BPO, 1%/5%, developed by Stiefel Laboratories, Inc. (currently a company of GlaxoSmithKline) as the first topical product in this class, was first approved in 1999 in Mexico. However, it has been reported that BPO causes skin irritation symptoms associated with erythema, skin exfoliation, and pruritus by stimulating the skin in a concentration-dependent manner,[9),10)] and that the efficacy of BPO appears to remain mostly unchanged over its concentration range of 2.5 to 10%.[11)] Accordingly, the product containing 3% BPO was developed and was first approved in Canada in April 2012 as a topical product to be used once daily. As of August 2014, this product is approved in a total of 16 countries including the United Kingdom (UK) and Germany.

The applicant has claimed the efficacy and safety of CLDM/BPO Gel, 1%/3%, were demonstrated in patients with acne vulgaris in clinical studies conducted in Japan from July 2011 and has recently submitted the new drug application.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug Substance (CLDM hydrate)

CLDM hydrate, a drug substance used in the drug product, is registered in the drug master file (MF Registration No. 226MF10069) by Union Quimico Farmaceutica, S.A. (Spain).

2.A.(1).1) Characterization

CLDM hydrate, a drug substance used in the drug product, is a white to slightly yellowish powder, and has been determined for descriptions, solubility, hygroscopicity, melting point, thermal analysis, optical rotation, pH, and polymorphism.

[4)] Takigawa M, *Hyojun Hifu Kagaku* ninth ed. 2010
[5)] Hayashi N, et al. *The Japanese Journal of Dermatology.* 2001;111:1347-1355
[6)] Hayashi N, et al. *The Japanese Journal of Dermatology.* 2008;118:1893-1923
[7)] Thiboutot D and Gollnick H, *J Am Acad Dermatol.* 2009;60:S1-S50
[8)] Nast A, et al. *JEADV.* 2012;26(Suppl. 1):1-29
[9)] Mills OH, et al. *Int J Dermatol.* 1986;25:664-667
[10)] Sagransky M, et al. *Expert Opin Pharmacother.* 2009;10:2555-2562
[11)] FDA, *Federal Register*, USA. 75 FR 9767. 2010

The chemical structure of CLDM hydrate, a drug substance, has been confirmed by mass spectrometry (MS), infrared spectrophotometry (IR), and nuclear magnetic resonance spectroscopy (^{1}H-NMR and ^{13}C-NMR), and thermal mass analysis. Thermal mass analysis revealed a mass loss of 3.39% after dehydration, which suggested that CLDM hydrate, a drug substance, is a mono-hydrate.

2.A.(1).2) Manufacturing process

See attachment (available only in Japanese).

2.A.(1).3) Management of CLDM hydrate

The proposed specifications for CLDM hydrate, a drug substance, include content, appearance, identification (IR and liquid chromatography [HPLC]), optical rotation, pH, purity (appearance of solution, related substances [HPLC], residual solvents (gas chromatography), water content, microbial limits, and assay (HLPC).

During the review process, specifications for purities in terms of heavy metals and arsenic were additionally included.

2.A.(1).4) Stability of CLDM hydrate

Table 1 summarizes the stability studies of CLDM hydrate, a drug substance.

Table 1. Stability studies of CLDM hydrate, a drug substance

Study	Primary batches	Temperature	Humidity	Duration of storage	Storage package
Long-term testing	3 commercial scale batches	25°C	60%RH	48 months	Double-layer polyethylene bags/Cardboard container
Accelerated testing	3 commercial scale batches	40°C	75%RH	6 months	

Consequently, a retest period of [redacted] years has been proposed for CLDM hydrate, a drug substance, when stored at room temperature in a low-density polyethylene pouch in a cardboard container. The long-term testing will be continued for [redacted] months.

2.A.(2) Drug Substance (BPO)

2.A.(2).1) Characterization

[redacted] Since BPO has an explosive nature, drug substance BPO contains water at a rate of [redacted]% or more to avoid the risk of ignition and explosion.

The chemical structure of BPO was confirmed with IR, nuclear magnetic resonance spectrum (^{1}H-NMR and ^{13}C-NMR), and ultraviolet visible absorption spectrum.

2.A.(2).2) Manufacturing process

[redacted]

The synthesis of benzoyl peroxide is defined as a critical step. [redacted]

2.A.(2).3) Management of BPO

[redacted]

2.A.(2).4) Stability of BPO

Table 2 summarizes the stability studies of BPO. The photostability testing revealed that BPO is photolabile.

Table 2. Stability studies of BPO, a drug substance

Study	Reference batches	Temperature	Humidity	Duration of storage	Storage package
Long-term testing	3 commercial scale batches	30°C	65%RH	12 months	low-density polyethylene pouch/ Sealed with a metal clip
Accelerated testing	3 commercial scale batches	40°C	75%RH	12 months	

Consequently, a retest period of [redacted] month has been proposed for BPO, a drug substance, when stored at ≤[redacted]°C in a low-density polyethylene pouch sealed with a metal clip in a cardboard container and thus protected from light. The long-term testing and accelerating testing will be continued for [redacted] months.

2.A.(3) Drug product

2.A.(3).1) Description and composition of the drug product and formulation development

The drug product is a viscous aqueous gel containing CLDM (1% clindamycin) and 3% BPO. The drug product also contains concentrated glycerin, carboxyvinyl polymer, dimethylpolysiloxane, hydrated silicon dioxide, polyoxyethylene (16) polyoxypropylene (30) glycol, sodium hydroxide, disodium edetate hydrate, disodium laureth sulfosuccinate, and purified water as excipients.

2.A.(3).2) Manufacturing process

[redacted]

2.A.(3).3) Control of drug product

[redacted]

2.A.(3).4) Stability of drug product

Table 3 summarizes the stability studies of the drug product.[12)] The photostability testing revealed that the drug product is photolabile.

Table 3. Stability studies of drug product

Study	Reference batches	Temperature	Humidity	Duration of storage	Storage package
Long-term testing	3 commercial scale batches	2 - 8°C	-	36 months	Polyethylene-laminated tube
Accelerated testing	3 commercial scale batches	25°C	60%RH	6 months	

Consequently, a shelf life of 36 months was proposed for the drug product when stored at a temperature between 2 to 8°C in a polyethylene-laminated tube and thus protected from light.

2.B. Outline of the review by PMDA

Based on the submitted data and the following review, PMDA concluded that the quality of the drug substances and drug product is appropriately controlled.

2.B.(1) Control of BPO-related substances

PMDA asked the applicant to explain the appropriateness of the control for related substances of the drug substance BPO, taking account of degradation pathways of BPO.

The applicant's explanation:

[redacted] The applicant explained that GSK-05, which is included in the specifications and test methods of BPO and controlled, was the only degraded product detected in stability testing of BPO, and no other degraded products were present at more than [redacted]%, suggesting the absence of an alternative degradation pathway.

The applicant concluded that related substances of the drug substance BPO are controlled appropriately.

[12)] Both the formulation made from the commercial batches used in the stability tests and the to-be-marketed formulation are of the same composition, but they are manufactured at different plants. Formulations manufactured in both plants conform to the same specifications.
[13)] Bach RD, et al. *J.Am.Chem.Soc.* 1996;118:12758-12765
[14)] Tu YP, et al. *Organic Mass Spectrometry.* 1993;28:1435-1439

PMDA' view:

BPO-related substances are controlled appropriately since benzoic acid and water are specified in the specifications and test methods for BPO.

2.B.(2) New excipients

The drug product contains polyoxyethylene (16) polyoxypropylene (30) glycol and disodium laureth sulfosuccinate. PMDA concluded that there are no particular problems with the use of these excipients for the following reasons.

2.B.(2).1) Specifications, test methods, and stability

The specifications and test methods for polyoxyethylene (16) polyoxypropylene (30) glycol were established according to the Japanese Pharmaceutical Excipients or other related standards. PMDA concluded that there are no particular problems with the stability of polyoxyethylene (16) polyoxypropylene (30) glycol, or the specifications and test methods, and stability of disodium laureth sulfosuccinate.

2.B.(2).2) Safety

Based on the submitted data, PMDA concluded that there are no particular problems in the safety of polyoxyethylene (16) polyoxypropylene (30) glycol and disodium laureth sulfosuccinate at the concentrations used in the drug product.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A. Summary of the submitted data

Clinical isolates obtained from patients with acne vulgaris enrolled in a Japanese phase III clinical study (Study STF115287) were used to determine their susceptibility to clindamycin phosphate (CLDM). Publications of primary pharmacodynamics studies of CLDM and benzoyl peroxide (BPO) were submitted as reference data. The applicant explained that no pharmacological studies were conducted for BPO because it has been used outside Japan since the 1960s for the treatment of acne vulgaris,[15)] and many results of its pharmacological studies are available.

Although the substances used in studies or referred to in publications mentioned in this section were not only clindamycin phosphate but also clindamycin hydroxide or other clindamycin compounds with unknown salt, CLDM in this section represents any of them.

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1) *In vitro* studies

[15)] Sagransky M, et al. *Expert Opin Pharmacother.* 2009;10:2555-2562

(a) Antimicrobial activity of CLDM against skin flora (5.3.5.1, Study STF115287)

Susceptibility of clinical isolates obtained from participants in a Japanese phase III study (Study STF115287) at baseline to CLDM was determined by the broth microdilution method proposed by the Clinical and Laboratory Standards Institute (CLSI). The results are summarized in Table 4.

Table 4. Susceptibility of clinical isolates obtained in Japanese phase III study (STF115287) to CLDM

Bacterial species (No. of isolates)	MIC range (μg/mL)	MIC_{90} (μg/mL)	Resistance rate (%)[a)] (No. of resistant isolates)
Propionibacterium acnes (*P. acnes*) (599 isolates)	≤0.06 - >128	2	9.3 (56)
Staphylococcus epidermidis (*S. epidermidis*) (361 isolates)	≤0.06 - >128	>128	41.8 (151)

CLDM concentration is expressed as that of clindamycin.
MIC range, the range of minimum inhibitory concentrations against strains isolated.
MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of strains tested.
a) Resistant breakpoint was set at MIC ≥8 μg/mL for *P. acnes*, and MIC ≥4 μg/mL for *S. epidermidis* according to the CLSI criteria.

(b) Development of antimicrobial resistance in *P. acnes* (4.2.1.1: Reference data: Ishida, 2008[16)]; Nakase, 2012[17)])

The applicant submitted published documents that report antimicrobial susceptibility of clinical isolates of *P. acnes* collected in Japan to various investigational drugs determined by the CLSI agar dilution method or the standard agar dilution method proposed by the Japanese Society of Chemotherapy. Table 5 summarizes the results reported.

Table 5. Antimicrobial susceptibility of clinical isolates of *P. acnes* collected in Japan

Investigational drugs	MIC range (μg/mL)		Resistance rate (%) (No. of resistant strains)		Resistance breakpoint[a)] (μg/mL)
	Isolated in 2006 and 2007[16)] (n = 48)	Isolated in 2008[17)] (n = 43)	Isolated in 2006 and 2007[16)] (n = 48)	Isolated in 2008[17)] (n = 48)	
CLDM	0.031 - ≥ 256	≤ 0.063 - ≥ 256	8.3 (4)	18.6 (8)	≥ 8
EM	0.063 - ≥ 256	≤ 0.063 - ≥ 256	10.4 (5)	20.9 (9)	≥ 2
CAM	0.063 - ≥ 256	≤ 0.063 - ≥ 256	10.4 (5)	20.9 (9)	≥ 2
JM	0.031 - ≥ 256	≤ 0.063 - ≥ 256	8.3 (4)	20.9 (9)	≥ 4
NDFX	0.125 - 1	≤ 0.063 - 4	0	0	≥ 8
LVFX	0.5 - 2	0.125 - 8	0	4.7 (2)	≥ 8
CDTR	0.063 - 0.5	≤ 0.063 - 0.25	0	0	≥ 64
FRPM	0.031 - 0.25	≤ 0.063	0	0	≥ 16

EM, erythromycin; CAM, clarithromycin; JM, josamycin; NDFX, nadifloxacin; LVFX, levofloxacin; CDTR, cefditoren; FRPM, faropenem
a) The resistance breakpoint was set according to the CLSI criteria.

(c) Antimicrobial activity of BPO (4.2.1.1: Reference data: Decker, 1989[18)]; Eady, 1994[19)]; Pannu, 2011[20)])

The applicant submitted published documents that report the antimicrobial activity of BPO against skin flora (*P. acnes* standard strain, EM-susceptible *Propionibacterium* spp. [including *P. acnes*] and *S. epidermidis*) and macrolide-resistant skin flora.[21)] The MICs and minimum bactericidal concentrations

[16)] Ishida N, et al. *Microbiol Immunol.* 2008;52:621-624
[17)] Nakase K, et al. *J Dermatol.* 2012;39:794-796
[18)] Decker LC, et al. *Antimicrob Agents Chemother.* 1989;33:326-330
[19)] Eady EA, et al. B*r J Dermatol.* 1994;131:331-336
[20)] Pannu J, et al. *Antimicrob Agents Chemother.* 2011;55:4211-4217
[21)] Macrolides such as EM have been used for the treatment of skin infection since the 1970s outside Japan, and the development of antimicrobial-resistant skin flora has been reported (Eady EA, et al. *Br J Dermatol.* 1994;131:331-336, Del Rosso JQ and Leyden JJ, *Dermatol Clin.* 2007;25:127-132).

(MBCs) of BPO against test strains were determined by the agar dilution method. Table 6 summarizes the results reported.

Table 6. Antimicrobial activity of BPO against skin flora

Bacterial species	No. of strains	BPO		EM	
		MIC range (μg/mL)	MBC range (μg/mL)	MIC range (μg/mL)	MBC range (μg/mL)
P. acnes standard strain[18)]	9	100 - 800	200 - 800	-	-
EM-susceptible *Propionibacterium* spp.[19)]	10	64 - 128	-	0.06 - 0.125	-
EM-resistant *Propionibacterium* spp.[19)]	10	64 - 128	-	512 - > 2048	-
EM-susceptible *S. epidermidis*[19)]	10	512	-	0.25 - 0.5	-
MS-resistant *S. epidermidis*[19)]	5	512	-	256 - 512	-
MLS-resistant *S. epidermidis*[19)]	5	512	-	> 2048	-

MS, Macrolide-streptogramin B; MLS, Macrolide-lincosamide-streptogramin B; -, not tested

Antimicrobial activity of BPO against *P. acnes* (3 standard strains, 2 CLDM-susceptible clinical isolates, 11 CLDM-resistant[22)] clinical isolates) was determined by the broth microdilution method. The MICs ranged from ≤50 to 100 μg/mL, and the MBCs ranged from 100 to 400 μg/mL.

(d) Effects of BPO on the generation of reactive oxygen species by polymorphonuclear leukocytes (4.2.1.1: Reference data; Hegemann, 1994[23)])

It has been suggested that in acne vulgaris, neutrophils infiltrating into the skin generate reactive oxygen species (ROS) that damage the hair follicle wall and exacerbate inflammation.[24)] It also has been reported that drugs for the treatment of staphylococcal skin infection exert their effects not only through inhibiting the growth of causative organisms but also by blocking the generation of ROS by human polymorphonuclear leukocytes (PMNLs).[25)] The applicant submitted published documents on the effect of BPO on the generation of ROS by PMNLs. BPO inhibited the generation of ROS by PMNLs in a concentration-dependent manner, and the 50% inhibitory concentration (IC_{50}) was 12.7 μmol/L.

(e) Antimicrobial activity of CLDM and BPO against isolated skin flora (4.2.1.1: Reference data; Dhillon, 2013[26)])

The applicant submitted a published document that describes the percentage of isolated skin flora (*P. acnes*, *S. epidermidis*, S*taphylococcus aureus*, and *Micrococcus* spp.) that are resistant to CLDM, BPO, and CLDM/BPO according to the inhibition zone diameters.[27)] In this study, the clinical isolates were collected from 50 patients with acne vulgaris in foreign countries in 2012 and 2013. The percentages of isolates resistant to CLDM, BPO, and CLDM/BPO were 50%, 25%, and 34%, respectively.

[22)] The resistance breakpoint, which was set according to the European Committee on Antimicrobial Susceptibility Testing, was MIC ≥0.25 μg/mL.
[23)] Hegemann L, et al. Br *J Dermatol.* 1994;130:569-575
[24)] Briganti S and Picardo M, *J Eur Acad Dermatol Venereol.* 2003;17:663-669
[25)] Miyachi Y, et al. *J Invest Dermatol.* 1986;86:449-453
[26)] Dhillon KS and Varshney KR, *Sch J App Med Sci.* 2013;1:724-727
[27)] A clinical isolate was determined resistant to a test substance when the zone of growth inhibition was ≤17 mm.

(f) Antimicrobial activity of a combination of CLDM and BPO against *P. acnes* (4.2.1.1: Reference data; Leyden, 2001[28])

The applicant submitted a published document that describes a study of the antimicrobial activity of CLDM and CLDM/BPO combination against *P. acnes*. The study was conducted in a total of 73 non-Japanese male and female healthy adult volunteers with *P. acnes* counts $\geq 10^4$ colonies/cm^2 on the forehead. The participants applied a CLDM/BPO gel, 1%/5%, or one of three different 1% CLDM topical formulations (gel, lotion, liquid) once daily for 2 weeks, and *P. acnes* counts at baseline, and after 1 week and 2 weeks of treatment were determined. Table 7 summarizes the results.

Table 7. *P. acnes* counts after treatment with CLDM/BPO gel, 1%/5%, or 1% CLDM topical formulations in humans

	CLDM/BPO gel, 1%/5% (n = 17)	1% CLDM topical formulations		
		Gel (n = 20)	Lotion (n = 19)	Liquid (n = 17)
Baseline cell count (log_{10}/cm^2)	6.32 ± 0.51	6.05 ± 0.61	6.24 ± 0.59	6.15 ± 0.64
Log reduction after 1 week[a)] (log_{10}/cm^2) (Reduction rate, %)	2.71 ± 0.63 (99.7)	0.16 ± 0.41 (30)	0.36 ± 0.49 (56)	0.47 ± 0.40 (62)
Log reduction after 2 weeks[a)] (log_{10}/cm^2) (Reduction rate, %)	3.08 ± 0.95 (99.9)	1.03 ± 1.04 (89)	0.91 ± 0.68 (88)	1.34 ± 0.64 (94)

Mean ± standard deviation (SD)
a) Difference in log viable count from baseline to each time point

3.(i).A.(1).2) *In vivo* studies (4.2.1.1)

(a) Effects of BPO on the removal of stratum corneum and comedone reduction in a mouse model of comedones (Reference data; Kligman, 1979[29])

The applicant submitted a published document that describes the effects of BPO on the removal of stratum corneum and comedones reduction in a mouse model of spontaneous comedones. In this study, (i) vehicle, (ii) 10% BPO, (iii) 0.05% tretinoin, which inhibits keratinization and comedones formation (the positive control), or (iv) 10% salicylic acid, which is used to remove horny cells, was applied to the back of rhino mice[30] in each group twice daily, 5 days a week, for 3 weeks. After the treatment period, the form of pseudocomedones and keratinization of the skin tissues at the application site were observed. Animals in the vehicle control group showed an enlargement of pseudocomedones with greater compaction of the horny masses and thickened stratum corneum suggestive of hyperkeratosis. Animals in the 10% BPO group showed thickening of the stratum corneum, but the size of the pseudocomedones did not increase. In the 0.05% tretinoin group, the pseudocomedones disappeared, and the stratum corneum did not thicken. In the 10% salicylic acid group, the appearance of the pseudocomedones did not change, but reduction of horny masses was observed.

[28)] Leyden J, et al. *Am J Clin Dermatol.* 2001;2:263-266
[29)] Kligman LH and Kligman AM, *J Invest Dermatol.* 1979;73:354-358
[30)] The rhino mouse, a variant of the hairless mouse, has been used as a model of acne as utriculi are derived from the infundibular zone of the initial follicular units and are histologically similar to comedones (Nieves NJ, et al. *J Invest Dermatol.*, 2010; 130: 2359-2367).

(b) The effects of BPO on the removal of stratum corneum and comedones reduction in a rabbit model of comedones (Reference data; Mills, 1975[31])

The applicant submitted a published document that describes the effects of BPO on the removal of stratum corneum and comedones reduction in a rabbit model of comedones induced by coal tar. In this study, 1% coal tar preparation was applied to bilateral external auditory canals of rabbits once daily, 5 days a week, for 2 weeks to induce comedones. From 3 days after the final application, unilateral external auditory canal of rabbits in each group was treated with 5% BPO, 10% BPO, or 0.05% tretinoin as the positive control, once daily, 5 days a week, for 2 weeks. The size of comedones was measured 3 days after the final treatment. Comedones covered with horny masses were observed in untreated external auditory canals. The size of comedones reduced as much as approximately 50% in animals treated with 5% BPO or 10% BPO, and epithelial hyperplasia suggestive of reduction of horny masses was also observed. In the 0.05% tretinoin group, comedones disappeared completely.

(c) The effects of BPO on the removal of stratum corneum and comedones reduction in a dog model of comedones (Reference data; Loux, 1974[32])

The applicant submitted a published document on the effects of BPO on the removal of stratum corneum and comedones reduction in a dog model of spontaneous comedones. In this study, preparations of 10% BPO, 3% salicylic acid, 0.1% tretinoin, or the respective vehicle were applied to follicular plugs on the back of dogs at least once daily for 14 to 21 days, and then the amount of horny plugs within hair follicles were assessed. Removal of stratum corneum was not observed in any vehicle control groups or the salicylic acid group, but was observed slightly in the 10% BPO group and substantially in the 0.1% tretinoin group.

(d) Sebo-suppressive effect of BPO (Reference data; Gloor, 1980[33])

It has been reported that acne vulgaris is associated with the overgrowth of *P. acnes*, a skin bacterium that feeds on sebum, in the skin with excessive secretion of sebum by sebaceous glands stimulated by various factors.[34),35),36)] The applicant submitted a published document that reports the effect of BPO on sebaceous glands. In this study, hamsters received treatment with 10% BPO preparation on one ear auricle and with the vehicle on the contralateral auricle. The preparation was applied every 3 days, 10 times in total. One day after the last treatment, the sebaceous gland density in the total treated area, the percentage of [^{3}H] thymidine-labeled sebaceous gland cells, and the number of sebaceous gland cells in metaphase were measured to be lower in the 10% BPO group than in the vehicle control group by 36%, 11%, and 34%, respectively.

3.(i).A.(2) Secondary pharmacodynamic studies

No study data were submitted in this application.

[31)] Mills OH Jr and Kligman AM, *Animal Models in Dermatology.* 1975;176-183
[32)] Loux JJ, et al. *J Soc Cosmet Chem.* 1974;25:473-479
[33)] Gloor M, et al. *Arch Dermatol Res.* 1980;267:97-99
[34)] Funasaka Y, et al. *Biyo Hifu Kagaku*. 2009;579-590
[35)] Beylot C, et al. *J Eur Acad Dermatol Venereol.* 2014;28:271-278
[36)] Berson DS and Shalita AR, *J Am Acad Dermatol.* 1995;32:S31-41

3.(i).A.(3) Safety pharmacology studies

No study data were submitted in this application.

The applicant's explanation:

In an *in vitro* study in isolated human skin, the total amount of BPO that penetrated into the skin after application was minimal.[37)] It is known that BPO applied to the skin is rapidly decomposed into benzoic acid in the skin tissues, and in a study of Japanese patients with acne vulgaris, the plasma concentration of benzoic acid was below the lower limit of quantification (100 ng/mL) in most patients.[38)] These findings suggest that BPO exerts its effect on the skin tissues, and that systemic exposure to benzoic acid, a decomposed product of BPO, is minimal. It is thus unlikely that BPO applied to the skin or its metabolites may affect the central nervous, respiratory, or cardiovascular system in routine clinical use.

3.(i).B Outline of the review by PMDA

3.(i).B.(1) Mechanism of action of BPO in the treatment of acne vulgaris and the effect of CLDM/BPO combination

The applicant's explanation on the mechanism of action of BPO:

Acne lesions are classified into inflammatory lesions (red papules, pustules, cysts, nodules) and non-inflammatory lesions (open and closed comedones), and abnormal lipid metabolism, hornification disorder, and overgrowth of skin flora are involved in the pathogenesis. *P. acnes*, the bacterium responsible for acne vulgaris, is considered to grow in hair follicles with excess sebum and cause comedones,[35),36)] cause neutrophil chemotaxis to recruit neutrophils into the affected hair follicles, and cause inflammation in hair follicles through the release of ROS by neutrophils. *P. acnes* is also considered to produce a bacterial lipase that is reported to be involved in inflammation in hair follicles and excessive keratinization in the hair follicle infundibulum.[34),35),36)] It has been also reported that *S. epidermidis*, a skin bacterium isolated from inflammatory lesions, may play a role in worsening inflammatory comedones,[16),39),40)] although no consensus has been reached on the role of *S. epidermidis* in the pathophysiology of acne vulgaris.

BPO, a highly lipophilic drug, distributes mainly into bacterial membranes to oxidize membrane proteins and other substances.[41),42),43)] In the skin, BPO is considered to produce ROS during the decomposition into benzoic acid[42),44)] and induce oxidative damages in membrane proteins and DNA of bacteria, and thereby exert non-specific antimicrobial action.[10),45)] In *in vitro* studies, BPO exerted an antimicrobial activity against CLDM-resistant *P. acnes* strains to a similar extent as against *P. acnes*

---

37) The total amount of BPO that penetrated into the skin after an application of ^{14}C-labeled BPO to the skin was only 4.5% of the total dose, and the remaining 95.5% of the dose remained on the skin [see "3.(ii).A.(2).1) BPO"].

38) Findings in a phase I study where Japanese patients with acne vulgaris were treated topically with CLDM/BPO Gel, 1%/3%, at a dose of 0.7 g twice a day for 7 days [see "4.(iii).A.(1) Japanese phase I study"].

39) Fitz-Gibbon S, et al. *J Invest Dermatol.* 2013;133(9):2152‑2160

40) Moon SH, et al. *J Dermatol.* 2012;39(10):833-837

41) Burkhart CN, et al. *SkinPharmacol Appl Skin Physiol.* 2000;13:292-296

42) Cove JH and Holland KT, *J Appl Bacteriol.* 1983;54:379-382

43) Valacchi G, et al. *Toxicology*. 2001;165:225-234

44) Tanghetti EA and Popp KF, *Dermatol Clin.* 2009;27 17-24

45) Avery SV, *Biochem J.* 2011;434:201-210

standard strains, and exerted against MS or MLS-resistant *S. epidermidis* strains to a similar extent as against EM-susceptible *S. epidermidis* strains. These results indicate that BPO is also effective against drug-resistant strains. Furthermore, no reports have suggested the development of BPO-resistant strains although BPO has been used in many foreign countries for the treatment of acne vulgaris since the 1960s.[15)]

In patients with acne vulgaris, keratinocytes in the infundibulum are activated, and thickening of the stratum corneum (hyperkeratosis) develops as a result of delayed desquamation or hyperplasia of the stratum corneum. These changes cause accumulation of stratum corneum and sebum, which induce the formation of microcomedones.[46)] In studies in an *in vivo* model of comedones, BPO induced the removal of stratum corneum and decreased the number of comedones at concentrations of ≥5% [see "3.(i).A.(1).2) *In vivo* studies"]. Since BPO is considered to inhibit the secretion of sebum by inhibiting the growth of sebaceous gland cells, BPO may decrease the amount of sebum in comedones by inhibiting sebum production, and thereby inhibit the growth of *P. acnes*, a bacterium that feeds on sebum. It has been suggested that neutrophils produce ROS that damage the hair follicle wall and thereby worsen inflammation.[47)] Because BPO inhibits PMNLs from releasing ROS in a concentration-dependent manner, it may exert an antiinflammatory effect by preventing ROS from destructing hair follicle wall.

The applicant's explanation on the effect of CLDM/BPO combination:
In a study of CLDM/BPO combination effects on clinical isolates of *P. acnes* collected from patients with acne vulgaris, the percentage of isolates susceptible to the presence of CLDM and BPO (66%) was higher than the percentage of isolates susceptible to the presence of CLDM alone (50%) [see "3.(i).A.(1) *In vitro* studies"]. These results indicate that BPO exerts an antimicrobial activity against some CLDM-resistant skin flora. In a study in which a CLDM/BPO gel, 1%/5%, or 3 topical agents of 1% CLDM was applied topically to non-Japanese healthy adult male and female volunteers once daily for 2 weeks, the numbers of *P. acnes* after 1 week and 2 weeks of treatment were lower in patients receiving the CLDM/BPO gel, 1%/5%, than in those receiving 1% CLDM topical agents [see "3.(i).A.(1) *In vitro* studies"]. It has been reported that the number of *P. acnes* at the application site was lower in subjects receiving a preparation containing CLDM and BPO than in those receiving a preparation containing BPO alone.[48)]

Study findings indicate that BPO exerts an antimicrobial action against *P. acnes*, the bacterium responsible for acne vulgaris, and against *S. epidermidis*, an organism suggested to play a role in the pathophysiology of acne vulgaris. BPO is, thus, effective in promoting the removal of stratum corneum and comedones reduction, inhibiting the production of sebum, and inhibiting human PMNLs from releasing ROS. Consequently, BPO is effective in reducing not only inflammatory lesions (red papules and pustules), but also non-inflammatory lesions (closed and open comedos). A combination of CLDM and BPO is also expected to be effective.

[46)] Thiboutot DM, *J Dermatol Treat.* 2000;11:S5-S8
[47)] Briganti S and Picardo M, *J Eur Acad Dermatol Venereol.* 2003;17:663-669
[48)] Leyden JJ, *Sem Cut Med Surg.* 2001;20:139-143

PMDA's view:

BPO is consider to exert a beneficial effect in the treatment of non-inflammatory and inflammatory lesions through exerting antimicrobial activity and inducing the removal of stratum corneum, among other actions. Published documents submitted by the applicant demonstrate the efficacy of combining CLDM with BPO.

3.(i).B.(2) Resistance to CLDM

PMDA asked the applicant to explain change in susceptibility of *P. acnes*, the bacterium responsible for acne vulgaris, to CLDM over the course of time.

The applicant's explanation:

Table 8 summarizes changes in susceptibility of clinical isolates of *P. acnes* to CLDM over the course of time in Japan. No substantial changes over time have occurred. The resistance rate of *P. acnes* to CLDM[49] was reported to be 79% in the United States (US) in 1983, 91% in Spain in 2003, 55.5% in the UK in 2003, and 53.5% in Hong Kong in 2013,[50] which were all higher than that in Japan.

Table 8 Changes over time in susceptibility of *P. acnes* to CLDM in Japan

Year of isolation	No. of strains	MIC range (μg/mL)	MIC_{90} (μg/mL)	Percentage of resistant strains[b]
1992 - 1993[51]	17	0.05 - > 100	0.4[a]	17.6%
1993 - 1997[52]	378	≤ 0.025 - > 400	0.05	1.85%
1994 - 1995[53]	50	0.025 - 50	0.2[a]	4%
1996 - 1997[54]	21	≤ 0.025 - 0.2	-	-
1996[55]	100	0.05 - 50	0.39	-
2000[55]	30	0.20 - 0.78	0.78	-
2005[55]	70	0.05 - 6.25	0.39	-
2006 - 2007[56]	48	0.031 - ≥ 256	1	8.3%
2008[57]	43	0.063 - ≥ 256	-	18.6%
2009 - 2010[58]	69	≤ 0.06 - ≥ 256	128	18.8%
2009 - 2010[59]	30	≤ 0.008 - 0.25	0.5	-
2011 - 2012[60]	599	≤ 0.06 - > 128	2	9.3%

-, Not tested

a) MIC_{80} (μg/mL)

b) Resistance breakpoint was set at ≥8 μg/mL (Resistance breakpoint for isolates collected from 1993 to 1997 was set at ≥3.13 μg/mL).

PMDA's view:

In Japan, susceptibility of *P. acnes*, the bacterium responsible for acne vulgaris, to CLDM has not changed substantially over time, and the resistance rate remains low in Japan as compared with other

[49] The resistance rate was reported as the percentage of resistant isolates in all isolates tested, or as the percentage of patients who had at least one strain of resistant *P. acnes* in patients from whom *P. acnes* had been isolated.
[50] Dreno B, et al. *Eur J Dermatol.* 2014; doi:10.1684/ejd.2014.2309
[51] Nishijima S, et al. *J Dermatol.* 1994;21:166-171
[52] Interview Form of Dalacin T Gel 1%. 2012
[53] Kurokawa I, et al. *Eur J Dermatol.* 1999;9(1):25-28
[54] Nishijima S, et al. *J Dermatol.* 2000;27:318-323
[55] Matsuzaki K, et al. *Jpn J Antibiotics.* 2006;59:316-319
[56] Ishida N, et al. *Microbiol Immunol.* 2008;52:621-624
[57] Nakase K, et al. *J Dermatol.* 2012;39:794-796
[58] Nakase K, et al. *J Med Microbiology.* 2014;63:712-718,
[59] Nakaminami H, et al. *Rinsho Iyaku*. 2012;28(1):65-72
[60] Clinical isolates obtained at baseline in the Japanese phase III study (Study STF115287).

countries. However, the percentage of *P. acnes* resistant to CLDM was reported to have rapidly increased over approximately 10 years from the 1980s to 1990s in foreign countries,[50),61)] and it cannot be ruled out that the percentage of *P. acnes* resistant to CLDM may increase in Japan in the future, which may affect the efficacy of CLDM/BPO Gel, 1%/3%. The applicant should continue to collect post-marketing information on resistance to CLDM, and appropriately provide the information to healthcare professionals in clinical settings when new findings become available.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A. Summary of the submitted data

CLDM/BPO gel, 1%/5%, was applied to the skin of mice to assess its percutaneous absorption. The skin penetration of CLDM/BPO Gel, 1%/3%, in human skin was assessed *in vitro*. Published documents describing the followings were submitted as reference data: the absorption, distribution, metabolism, and excretion of BPO in rabbits, rats, and monkeys receiving BPO percutaneously; *in vitro* human skin penetration of BPO; plasma protein binding of benzoic acid and hippuric acid[62)]; and pharmacokinetic drug interactions.

Since BPO is rapidly decomposed into benzoic acid in the skin tissues, benzoic acid concentrations in plasma and urine were determined.

In this section, the dose and concentration of CLDM are expressed in terms of those of clindamycin. Unless otherwise specified, all pharmacokinetic parameters are expressed as means.

3.(ii).A.(1) Absorption (4.2.2.2)

3.(ii).A.(1).1) BPO (Reference data; Sahut, 1985[63)])

Rabbits (n = 6/sex) received BPO gel at 500 mg/day percutaneously once daily for 33 days, and the pharmacokinetics of benzoic acid in plasma were evaluated.[64)] Plasma benzoic acid concentration 30 minutes after application on Days 5, 12, 19, 26, and 33 of treatment was 2538 ng/mL, which was higher than the intrinsic concentration[65)] by 1656 ng/mL. On Day 33, plasma benzoic acid concentration was only slightly higher than the intrinsic concentration, which indicates that benzoic acid is not accumulated during the repeated skin applications of BPO for 33 days.

[61)] Cooper AJ, *Med J Aust.* 1998;169(5):259-261

[62)] As BPO is metabolized into benzoic acid in the skin of animals, and is then metabolized into hippuric acid in the plasma in humans, BPO is not detected in plasma.

[63)] Sahut A, et al. *Int J Cosmet Sci.* 1985;7:61-69

[64)] Plasma benzoic acid concentration was determined with high-performance liquid chromatography with an ultraviolet absorption detector (lower limit of quantification: 250 ng/mL).

[65)] The body is exposed to benzoic acid derived from feeds. Plasma benzoic acid concentration immediately before an administration of BPO to the skin (882 ng/mL) was defined as the "intrinsic concentration."

3.(ii).A.(1).2) CLDM 1%/BPO 5% gel (Study 0470MS50.001)

Mice (n = 3/sex/group) received CLDM/BPO gel, 1%/5%, at 4/20, 12/60, 40/200, or 80/400 (CLDM/BPO) mg/kg/day percutaneously once daily for 28 days. Pharmacokinetic parameters[66] of benzoic acid and CLDM in plasma are summarized in Table 9. The C_{max} and AUC_{0-t} on Day 7 of treatment generally increased with increasing dose. Plasma exposure to CLDM generally increased dose-proportionally in the 40/200 mg/kg/day or lower dose groups. No findings suggested the accumulation of CLDM associated with repeated applications of CLDM/BPO.

The C_{max} and AUC_{0-t} in female mice were higher than those in male mice, while glomerular filtration rate was lower in females than in males.[67] It has been reported that benzoic acid is a substrate of organic anion transporter (OAT) 1 in mice, and the renal expression level of OAT1 protein in females is approximately 1/4 of that in males.[68] On the basis of these findings, the applicant explained that the differences in C_{max} and AUC_{0-t} between male and female mice reflect the lower renal clearance of benzoic acid in females than in males.

Table 9. Pharmacokinetic parameters of benzoic acid and CLDM in mice receiving CLDM/BPO gel, 1%/5%, percutaneously repeatedly

Day of treatment	Sex	Dose [a] (mg/kg/day)	Benzoic acid			CLDM		
			C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-t} (ng·hr/mL)	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-t} (ng·hr/mL)
7	Male	4/20	ND	ND	ND	18.2	0.5	43.0
		12/60	ND	ND	ND	41.5	0.5	134.2
		40/200	346	3.0	962	141.7	0.5	429.8
		80/400	665	0.5	757	260.3	0.5	1652
	Female	4/20	ND	ND	ND	7.9	1.0	19.2
		12/60	461	3.0	882	36.6	1.0	88.8
		40/200	712	1.0	2401	75.3	0.5	362.5
		80/400	951	3.0	6306	305.6	1.0	1156
28	Male	4/20	ND	ND	ND	14.7	1.0	25.5
		12/60	ND	ND	ND	42.8	1.0	116.9
		40/200	ND	ND	ND	102.1	1.0	351.2
		80/400	1997	1.0	4654	350.1	0.5	1500
	Female	4/20	ND	ND	ND	12.3	0.5	23.6
		12/60	ND	ND	ND	56.7	0.5	63.0
		40/200	ND	ND	ND	50.2	1.0	163.9
		80/400	2924	1.0	7387	256.7	3.0	1113

Mean; ND, not detected
C_{max}, Maximum plasma concentration; t_{max}, Time to the maximum plasma concentration
AUC_{0-t}, Area under the curve from time 0 to the last sampling time
a) CLDM/BPO

3.(ii).A.(2) Distribution (4.2.2.3)

3.(ii).A.(2).1) BPO (Reference data: Nacht, 1981[69]; Wepierre, 1986[70])

In an *in vitro* study, 4.56 mg of ^{14}C-labeled BPO was applied as a 10% suspension to a stratum corneum chamber (5.08 cm^2) of human abdominal skin (700 to 800 μm thick). The distribution of BPO-related substances (BPO and benzoic acid) in the skin surface, skin tissues, and dermis was determined 8 hours

[66] Plasma benzoic acid concentration was determined by high-performance liquid chromatography with an ultraviolet absorption detector (lower limit of quantification: 250 ng/mL), and plasma CLDM concentration was determined by liquid chromatography-tandem mass spectrometry (lower limit of quantification: 0.5 ng/mL).
[67] Hackbarth H, et al. *Lab Anim.* 1981;15:267-272
[68] Breljak D, et al. *Am J Physiol Renal Physiol.* 2013;304:F1114-1126
[69] Nacht S, et al. *J Am Acad Dermatol.* 1981;4(1):31-37
[70] Wepierre J, et al. *Int J Cosmet Sci.* 1986;8:97-104

after administration.[71)] Of the total dose of BPO applied, the percentage of BPO-related substances recovered in the skin surface, skin tissues, and dermis was 95.5%, 2.6%, and 1.9%, respectively, indicating that 4.5% of the dose is distributed to the skin tissues during 8 hours after administration.

A single 10 mg dose of ^{14}C-labeled BPO gel was administered percutaneously to rats (3 males) to determine the distribution of BPO-related substances (BPO and benzoic acid) in the skin tissues at the administration site at 3, 8, and 24 hours after administration.[72)] At 3 hours after administration, 11.4%, 0.14%, 0.40% and 0.47% of the dose administered were present as BPO-related substances in the horny layer, epidermis, upper dermis, and deeper dermis. The amount of BPO-related substances in the horny layer accounted for 11.4%, 14.4%, and 17.1% of the dose at 3, 8, and 24 hours after administration. At 24 hours after administration, the amount of BPO-related substances present in the skin tissues accounted for 18.2% of the dose.

3.(ii).A.(2).2) CLDM/BPO Gel, 1%/3% (Study 2008-350-MB)

In an *in vitro* study, CLDM/BPO Gel, 1%/3%, or CLDM/BPO gel, 1%/5%, was applied at 15.63 mg/cm^2 (containing 0.16 mg/cm^2 of CLDM and 0.47 or 0.78 mg/cm^2 of BPO when the 3% BPO or 5% BPO preparations were used) to the surface (0.64 cm^2) of human abdominal skin approximately 0.25 mm thick to assess skin permeability of clindamycin (as the sum of clindamycin as a hydrolysate and clindamycin-equivalent amount of the phosphate), BPO, and benzoic acid[73)] 6 hours after application.[74)] Table 10 lists the amount of substances recovered in the receptor chamber during 6 hours after application and those present in the epidermis and dermis at 6 hours after application.

Table 10. Amounts of substances retrieved in the receptor chamber after an application of CLDM/BPO gel on human skin sample and those present in the epidermis and dermis

	Compound	Epidermis (μg)	Dermis (μg)	Receptor chamber (μg)
Product (CLDM/BPO, 1%/3%)	Clindamycin[a)]	12.47 ± 2.48	1.78 ± 0.43	0.19 ± 0.07
	BPO	18.22 ± 4.38	2.64 ± 0.62	BQL
	Benzoic acid	1.70 ± 0.17	1.37 ± 0.20	1.13 ± 0.11
CLDM/BPO, 1%/5%	Clindamycin[a)]	6.73 ± 2.04	1.14 ± 0.30	0.17 ± 0.07
	BPO	18.43 ± 6.75	2.65 ± 0.74	BQL
	Benzoic acid	2.11 ± 0.29	1.81 ± 0.35	2.49 ± 0.25

Mean ± standard error
CLDM/BPO Gel, 1%/3%, was applied to 28 samples, while the CLDM/BPO gel, 1%/5%, was applied to 26 samples.
BQL, below the quantification limit
a) Sum of clindamycin after hydrolysis and clindamycin equivalent amount of clindamycin phosphate

[71)] A human abdominal skin sample was set into a diffusion cell system, and ^{14}C-labeled BPO was applied to the skin surface. Substances that cross the skin are retrieved into a receptor chamber. The distribution of substances was analyzed by thin layer chromatography and autoradiography.
[72)] At 3, 8, and 24 hours after application of ^{14}C-labeled BPO on the skin of rats, the skin at the application site was obtained and was analyzed for the amount (mass) of the substance in different skin layers by thin layer chromatography and autoradiography.
[73)] BPO is metabolized into benzoic acid, and CLDM is metabolized into clindamycin.
[74)] A human abdominal skin sample is set in an in-line diffusion cell system, and CLDM/BPO Gel, 1%/3%, or a CLDM/BPO gel, 1%/5%, was applied on the skin sample. Substances penetrated into the skin were retrieved in the receptor chamber.

3.(ii).A.(3) Metabolism (4.2.2.3)

BPO (Reference data: Wepierre, 1986[70]; Nacht, 1981[69])

A single dose of 10 mg ^{14}C-labeled BPO gel was administered percutaneously to rats (3 males) to determine the distribution of metabolites in the horny layer, epidermis, and dermis.[75] In the horny layer, BPO recovered ranged from 9.3% (3 hours after administration) to 13.8% (24 hours after administration) of the dose administered, and benzoic acid recovered ranged from 2.1% (3 hours after administration) to 4.3% (8 hours after administration) of the dose administered. In the epidermis and dermis, only 0.04% to 0.18% of the dose administered was present as BPO, and 0.8% to 1.1%, which accounts for approximately 59% and 74% of the radioactivity (BPO and benzoic acid) remaining in the epidermis and dermis, was present as benzoic acid. During the period from 3 to 24 hours after application, the ratio of benzoic acid to BPO was generally constant in all layers of the skin.

Rhesus monkeys (2 males, 1 female) received a single dose of 139 μg ^{14}C-labeled BPO percutaneously, and metabolites in the urine were determined. Benzoic acid accounted for ≥95% of BPO-related substances in the urine, and another 3 different metabolites were detected. As hippuric acid was detected in human plasma [see "4.(ii).A.(1) Japanese phase I study"], it was considered that benzoic acid in human plasma is partially metabolized into hippuric acid, which is excreted into the urine. Based on the above findings, BPO was assumed to be metabolized as shown in Figure 1.

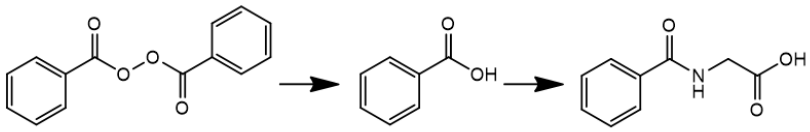


Figure 1. Possible metabolic pathway of BPO

3.(ii).A.(4) Excretion (4.2.2.3)

BPO (Reference data; Nacht, 1981[69])

Rhesus monkeys (2 males, 1 female) received a single dose of 139 μg ^{14}C-labeled BPO gel percutaneously, and urinary excretion of benzoic acid was determined. During the 7 days after administration, approximately 45% of the dose was excreted as benzoic acid into the urine. BPO-related substances were still detected in the urine in 2 of the 3 animals 6 days after administration but not detected in any animals 7 days after administration.

[75] At 3, 8, and 24 hours after application of ^{14}C-labeled BPO on the skin of rats, the skin at the application site was obtained and was analyzed for the mass of BPO and benzoic acid in different skin layers by thin layer chromatography and autoradiography.

3.(ii).A.(5) Pharmacokinetic drug interactions (4.2.2.3, 4.2.2.4)

3.(ii).A.(5).1) Benzoic acid (Reference data: Eraly, 2006[76]; Tamai, 1999[77]; Pfennig, 2013[78])

Potential as a substrate or inhibitor for transporters

In a study in OAT1 knock-out mice, benzoic acid was considered a substrate of OAT1 in mice. In a study in MDA-MB231 cells transfected with rat monocarboxylic acid transporter (MCT) 1, benzoic acid was considered a substrate of MCT1 in rats. In HEK293 cells transfected with rat or human OAT2, no OAT2-mediated transport of benzoic acid was observed.

In a study in Xenopus laevis oocytes transfected with mouse OAT1, benzoic acid inhibited the transport of para-aminohippuric acid, a substrate of OAT1, with an inhibition constant (K_i) of 30.9 μg/mL.

3.(ii).A.(5).2) Hippuric acid (Reference data: Deguchi, 2004[79]; Deguchi, 2006[80]; Fujita, 2014[81]; Mutsaers, 2011[82]; Tsujimoto[83]; Volpe[84])

(a) Potential as a substrate and inhibitor for transporters

In a study in HEK293 cells transfected with human OAT1 gene (hOAT1) or human OAT3 gene (hOAT3) to examine whether these cells uptake hippuric acid or not, hippuric acid was considered to be a substrate of OAT1, but not a substrate of OAT3.

In a study in Xenopus laevis oocytes transfected with rat organic anion transporter polypeptide (OATP) 2 gene, no OATP2-mediated transport of hippuric acid into Xenopus laevis oocytes was observed.

In a study in HEK293 cells transfected with hOAT1 or hOAT3, the effects of hippuric acid on the transport of para-aminohippuric acid or benzylpenicillin (PCG), a substrate of OAT3, were investigated. Hippuric acid inhibited the transport of para-aminohippuric acid via OAT1 with a K_i of 3.37 μg/mL and the transport of PCG via OAT3 with a K_i of 5.52 μg/mL.

In a study in HEK293 cells transfected with OATP1B1, hippuric acid inhibited the transport of SN-38, a substrate of OATP1B1, with an IC_{50} of 1202 μg/mL. In a study in HEK293 cells transfected with multidrug resistance-associated protein (MRP) 4 or breast cancer resistance protein (BCRP), hippuric acid inhibited the transport of methotrexate via MRP4 with an IC_{50} of 177.4 μg/mL and the transport of estrone sulfate via BCRP with an IC_{50} of 657.6 μg/mL.

[76] Eraly SA, et al. *J Biol Chem.* 2006;281:5072-5083
[77] Tamai I, et al. *J Pharm Pharmacol.* 1999;51:1113-1121
[78] Pfennig T, et al. *Biochim Biophys Acta.* 2013;1828:491-498
[79] Deguchi T, et al. *Kidney Int.* 2004;65:162-174
[80] Deguchi T, et al. *J Neurochem.* 2006;96:1051-1059
[81] Fujita K, et al. *Pharm Res.* 2014;31:204-215
[82] Mutsaers HAM, et al. *PLoS ONE.* 2011;6:e18438
[83] Tsujimoto M, et al. *Ther Apher Dial.* 2014;18:174-180
[84] Volpe DA, et al. *Regul Toxicol Pharmacol.* 2014;68:297-303

(b) Inhibition of CYP isoenzymes

In a study in human liver microsomes, the effects of hippuric acid on CYP1A2 and CYP2D6 were investigated. Hippuric acid did not affect their activities. In a study to investigate the effect of hippuric acid on CYP3A4 with testosterone metabolism as a marker, hippuric acid inhibited testosterone metabolism with an IC_{50} of 129 to 241.9 μg/mL.

3.(ii).B Outline of the review by PMDA

PMDA concluded that there were no particular problems with the results of non-clinical pharmacokinetic studies.

3.(iii) Summary of toxicology studies

3.(iii).A. Summary of the submitted data

The applicant submitted the following study results as evaluation data: repeated-dose dermal toxicity studies of CLDM/BPO gel, 1%/5%, in rats and mini pigs; a 2-year dermal carcinogenicity study and a photocarcinogenicity study of CLDM/BPO gel, 1%/5%, in mice; and an eye irritation study of CLDM/BPO Gel, 1%/3%, in rabbits. The applicant also submitted published documents of the following studies of BPO as reference data: single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproduction toxicity studies, eye and skin local irritation studies, skin sensitization studies, and photocarcinogenicity studies. No new study results were submitted for CLDM. In this section, the concentration and dose of CLDM are expressed in terms of those of clindamycin.

3.(iii).A.(1) Single dose toxicity studies (4.2.3.1: Reference data: OECD SIDS, 2002[85]; Federal Register, 1982[86])

No data of single-dose toxicity studies of CLDM/BPO Gel, 1%/3%, were submitted in this application.

The approximate lethal dose of BPO has been determined to be >2000 mg/kg and >3000 mg/kg in mice and rats, respectively, receiving the drug orally, and >1000 mg/kg in guinea pigs receiving the drug percutaneously.

3.(iii).A.(2) Repeated-dose toxicity studies (4.2.3.2: 93G-2325.1, 0470PS.50.001: Reference data; Federal Register, 1982[86])

The applicant submitted the study results of repeated-dose dermal toxicity of CLDM/BPO gel, 1%/5%, in rats (for 28 days), and mini pigs (90 days). No systemic effects were observed in rats or mini pigs. Local reactions observed in these studies were skin erythema in rats. The applicant submitted, as reference data,[86] the results of a 3-month oral toxicity study of BPO in rats and 43-day and 3-month dermal toxicity studies of BPO in rabbits. Rats in the 2000 mg/kg group showed anorexia, exhaustion,

[85] OECD SIDS, BENZOYL PEROXIDE CAS No: 94-36-0. 2002
[86] Federal Register. 1982;47(56):p.12443

and body weight reduction. Rabbits did not show systemic reactions, but had skin erythema.[87] It was concluded that the systemic toxicity observed and toxicity of metabolites such as benzoic acid and hippuric acid in rats receiving BPO orally are not relevant in terms of safety to humans when BPO is percutaneously administered for the following reasons: Since CLDM/BPO Gel, 1%/3%, is applied to the skin, BPO absorbed from the human skin surface is metabolized into benzoic acid and hippuric acid [see "BPO" in 3.(ii).A.(3) Metabolism]; Benzoic acid, a BPO metabolite, is found in foods and taken regularly, and is served as a food additive with an acceptable daily intake (ADI) of 5 mg/kg/day;[88] in a phase I study (Study STF115959) of CLDM/BPO Gel, 1%/3%, plasma exposures (C_{max} and AUC) to benzoic acid and hippuric acid on Day 8 of treatment were similar to baseline values.

3.(iii).A.(2).1) Repeated-dose dermal toxicity study of CLDM 1%/BPO 5% gel in rats (4.2.3.2, 93G-2325.1)

CLDM/BPO gel, 1%/5%, at 0 (gel base), 80, 400, and 2000 mg/kg (0.8/4, 4/20, and 20/100 mg/kg as CLDM/BPO) was applied to the skin of SD rats (n = 10/sex/group) and occluded for 6 hours once daily for 28 days. No systemic toxicity was found, and skin erythema at the application site was noted in the ≥80 mg/kg groups. The NOAEL for systemic toxicity was determined to be 2000 mg/kg/day, and that for local toxicity was <80 mg/kg/day. The human equivalent dose of the NOAEL for systemic toxicity was 3.2 mg/kg for CLDM and 16.2 mg/kg for BPO,[89] which are approximately 6 and 10 times the expected clinical dose, respectively.[90]

3.(iii).A.(2).2) Repeated-dose dermal toxicity study of CLDM 1%/BPO 5% gel in mini pigs (4.2.3.2, 0470PS.50.001)

CLDM/BPO gel, 1%/5%, at 0 (gel base), 50, and 500 mg/kg (0.5/2.5 and 5/25 mg/kg as CLDM/BPO) was applied to the skin of mini pigs (n = 3/sex/group) and occluded for 6 hours once daily for 90 days. No systemic or local toxicities were observed. The NOAEL was determined to be 500 mg/kg/day. The human equivalent dose of the NOAEL for systemic toxicity was 4.7 mg/kg for CLDM and 23.6 mg/kg for BPO,[91] which are approximately 9 and 14 times the anticipated clinical dose, respectively.[90] The human equivalent dose of the NOAEL for local toxicity was 0.4 mg/cm^2 for CLDM and 2 mg/cm^2 for BPO,[92] which are approximately 6 and 10 times the expected clinical dose, respectively.[93]

---

[87] A 10% BPO lotion was applied to the skin at a dose of 240 mg/kg as BPO for 43 days, or a BPO ointment was applied to the skin at a dose of 83 mg/kg 5 days a week for 3 months.

[88] Many foods such as milk, dairy products, fruits, potatoes, and grains contain benzoic acid, and the estimated average daily intake of sodium benzoate ranges from 0.02 to 0.2 mg/kg in Japanese (*Concise International Chemical Assessment Document 26*. WHO; 2000).

[89] The human equivalent dose of 2000 mg/kg of CLDM/BPO gel, 1%/5%, was 3.2 mg/kg for CLDM (calculated by 20 mg/kg × [6 mg/m^2/37 mg/m^2]), and 16.2 mg/kg for BPO (100 mg/kg × [6 mg/m^2/37 mg/m^2]).

[90] On the basis of the results of the Japanese phase III clinical study (Study STF115288), the daily dose of CLDM/BPO was calculated as 0.55/1.66 mg/kg with an assumed maximum daily dose of the gel of 2.77 g when applied once daily and a body weight of 50 kg.

[91] The human equivalent dose of 500 mg/kg of CLDM/BPO gel, 1%/5%, was 4.7 mg/kg for CLDM [calculated by 5 mg/kg × (35 mg/m^2/37 mg/m^2)], and 23.6 mg/kg for BPO (25 mg/kg×[35 mg/m^2/37 mg/m^2]).

[92] Considering the body weight of a typical mini pig 20 kg and the application site 250 cm^2, the dose of CLDM/BPO was calculated as 0.4/2 mg/cm^2.

[93] On the basis of the results of the Japanese phase III clinical study (Study STF115288), the daily dose of CLDM/BPO was calculated as 0.07/0.21 mg/cm^2 with an assumed maximum daily dose of the gel of 2.77 g when applied once daily and a facial area of approximately 400 cm^2.

3.(iii).A.(3) Genotoxicity studies (4.2.3.3.1: Reference data: OECD SIDS, 2002[85]; Dillon, 1998[94]; Yavuz, 2010[95]; Saladion, 1985[96]: 4.2.3.3.2: Reference data; OECD SIDS, 2002[85])

No genotoxicity studies of CLDM/BPO Gel, 1%/3%, have been conducted.

BPO has been determined not to be genotoxic in bacterial reverse mutation assays, chromosomal aberration assays in Chinese hamster lung cells, or micronucleus tests in mice. In a chromosomal aberration assay in human lymphocytes, increased chromosomal aberration frequency was seen when treated with BPO at ≥25 μg/mL for 48 hours. In a DNA damage study in human bronchial epithelial cells, induced DNA fragmentation was observed when treated with BPO at 24.2 μg/mL for 1 hour. This is considered to be caused by oxidative DNA damage by BPO. The applicant explained that these changes are not biologically relevant as no neoplastic lesions were observed in 2-year repeated-dose dermal carcinogenicity studies of BPO in mice and rats [see "3.(iii).A.(4) Carcinogenicity studies"].

3.(iii).A.(4) Carcinogenicity studies

Reference data indicate no neoplastic lesions were observed in 2-year dermal carcinogenicity studies in mice and rats. Because squamous papilloma was observed in a short-term carcinogenicity study by dermal application in Tg.Ac mice,[97] BPO is considered to promote skin tumors. A 2-year carcinogenicity study by dermal application of CLDM/BPO gel, 1%/5%, was conducted in mice. No neoplastic lesions were observed. The dose of 8000 mg/kg/day of CLDM/BPO gel, 1%/5% (80/400 mg/kg/day as CLDM/BPO), at which no carcinogenic findings were observed, is equivalent to 0.4 mg/cm^2 CLDM and 2 mg/cm^2 BPO[98] for the unit area of the application site and approximately 6 and 10 times the expected clinical dose of CLDM and BPO, respectively.[93]

3.(iii).A.(4).1) Studies of BPO (4.2.3.4.1 and 4.2.3.4.2)

(a) 2-year dermal carcinogenicity study in mice (Reference data; CHPA, 2001[99])

B6C3F1 mice (n = 50/sex/group) received BPO gel percutaneously at 0 (gel base), 1, 5, and 25 mg[100] once daily for 2 years.[101] No findings of systemic toxicity or neoplastic lesions were observed. Non-neoplastic lesions observed in the study included acanthosis, hyperkeratosis, sebaceous hyperplasia, and subepidermal inflammation at the application site.

[94] Dillon D, et al. *Mutagenesis.* 1998;13(1):19-26
[95] Yavuz A, et al. *Turk J Biol.* 2010;34:15-24
[96] Saladino AJ, et al. *Cancer Res.* 1985 45: 2522-2526
[97] FVB/N mice transfected with an activated v-Ha-ras gene.
[98] Considering the body weight of a mouse 30 g and the application site 6 cm^2, the dose of CLDM/BPO was calculated as 0.4/2 mg/cm^2.
[99] Dermal oncogenicity study of benzoyl peroxide gels in mice, CHPA. 2001
[100] Treatment was suspended in the BPO 25 mg/day group at Week 57 of treatment due to application site ulcer. At Week 59, treatment was resumed at a dose of 15 mg/day. As application site ulcer continued, treatment was suspended at Week 85, and was resumed at 15 mg/day at Weeks 87 to 92. Treatment was suspended between Week 93 and the end of study.
[101] The test gel was applied topically to the shaved skin on the back. The application area was approximately 6 cm^2 and was not covered after application. A non-treatment control group was included in the study.

(b) 2-year dermal carcinogenicity study in rats (Reference data; CHPA, 2002[102])

F344 rats (n = 50/sex/group) received BPO gel percutaneously at 0 (gel base), 5, 15, or 45 mg once daily for 2 years.[103] No findings of systemic toxicity or neoplastic lesions were observed. Non-neoplastic lesions observed in the study were mild to moderate acanthosis, hyperkeratosis, sebaceous hyperplasia, and chronic subepidermal inflammation at the application site.

(c) Short-term carcinogenicity study in transgenic mice (Reference data; Spalding, 1993[104])

Groups of heterozygous Tg.AC mice and wild-type FVB/N male mice (n = 5/group) were given BPO percutaneously at 0 (acetone), 1, 5, or 10 mg twice weekly for 20 weeks. In the ≥5 mg groups, skin papilloma developed at Week 8 of treatment or thereafter. Homozygous Tg.AC mice (n = 3/sex/group) were given BOP percutaneously at 0 (acetone), 5, or 10 mg twice weekly for 20 weeks. In the 5 mg and 10 mg groups, skin papilloma developed at Week 6 or 7 of treatment or thereafter. The incidence of papilloma was higher in females than in males. BPO was considered to have a promoter activity.

3.(iii).A.(4).2) Studies of CLDM/BPO gel, 1%/5% (4.2.3.4.1)

(a) 13-week repeated-dose dermal toxicity studies in mice (0470MS.50.001)

In a dose-finding study for 2-year dermal carcinogenicity study in mice, CD-1 mice (n = 10/sex/group) were given CLDM/BPO gel, 1%/5%, percutaneously at 0 (gel base), 400, 1200, 4000, or 8000 mg/kg[105] (4/20, 12/60, 40/200, or 80/400 mg/kg as CLDM/BPO) once daily for 13 weeks.[106] No findings of systemic toxicity were observed. Animals in the ≥400 mg/kg groups showed an increase in incidence or severity of epithelial hyperplasia of skin, keratosis, and subcutaneous inflammation at the application site.

(b) 2-year dermal carcinogenicity study in mice (0475MS.50.001)

CD-1 mice (n = 50/sex/group) were given CLDM/BPO gel, 1%/5%, percutaneously at 0 (water), 0 (gel base), 1200, 4000, or 8000 mg/kg (12/60, 40/200, or 80/400 mg/kg as CLDM/BPO) once daily for 2 years.[107] Survival rate tended to be low in the 8000 mg/kg group, but no neoplastic lesions were found. Non-neoplastic lesions found in animals in the ≥1200 mg/kg groups included an increase in incidence or severity of epidermal hyperplasia, hyperkeratosis, fibrosis, mast cell infiltration, sebaceous hyperplasia, and ulcers at the application site. Similar findings were also found in the untreated skin area, although the incidence was lower than in the application site. The applicant explained that these findings might be caused by the test substances transferred to the surrounding untreated skin during grooming.

---

[102] Dermal oncogenicity study of benzoyl peroxide gels in rats, CHPA. 2002

[103] The test gel was applied topically to the shaved skin on the back. The application area was approximately 17.5 cm^2 and was not covered after application. A non-treatment control group was included in the study.

[104] Spalding JW, et al. *Carcinogenesis.* 1993;14:1335-1341

[105] The doses of 10, 30, 100, and 200 μL of CLDM/BPO gel, 1%/5%, per body weight were calculated with an animal body weight of 25 mg and a specific gravity for gel of 1.

[106] A non-treatment control group was included in the study.

[107] The test substance was applied to a shaved skin area of approximately 6 cm^2 without cover. The application site was washed with warm water every 5 to 7 days.

3.(iii).A.(5) Reproductive and developmental toxicity (4.2.3.5.1)

No reproduction toxicity studies of CLDM/BPO Gel, 1%/3%, were conducted.

In oral developmental toxicity studies of BPO, its effects on male and female fertility and on pre- and postnatal development were assessed, and the findings were toxic effects on male and female reproductive organs and small size and low body weight of offspring in the 1000 mg/kg group. The applicant explained that the reproductive or developmental toxicity observed in animals receiving BPO orally are not relevant in terms of safety to humans who use CLDM/BPO Gel, 1%/3%, topically for the following reasons: Since CLDM/BPO Gel, 1%/3%, is applied to the skin, BPO absorbed from the skin surface is metabolized to benzoic acid in the skin tissue [see "BPO" in 3.(ii).A.(3) Metabolism], it is unlikely that a substantial systemic exposure to BPO occurs; and benzoic acid, a BPO metabolite, is not considered teratogenic or does not exert reproductive or developmental toxicity.[108)]

Reproductive and developmental toxicity studies of BPO (Reference data; Song, 2003[109)])

SD rats (n = 10/sex/group) were received BPO orally at 0 (corn oil), 250, 500, or 1000 mg/kg once daily for 14 days before and 14 days during the mating period. In addition, female animals received oral dose of the substance for 21 days during pregnancy and 3 days postpartum. No deaths, abnormal clinical findings, or body weight changes were observed in paternal or maternal animals. In the 1000 mg/kg group, reduced weight and regressive changes of the testicles and epididymis,[110)] and endometrial hyperplasia and vacuolization were found. Pups in the 1000 mg/kg were small in size, and showed low body weight on postnatal day 3. On the basis of these results, the NOAEL for maternal and paternal general toxicity and reproductive performance, and that for pups were determined to be 500 mg/kg/day.

3.(iii).A.(6) Local tolerance studies (4.2.3.6: 1549-002: Reference data: Federal Register, 1982[111)]; Lorenzetti, 1977[112)]; Haustein, 1985[113)])

CLDM/BPO Gel, 1%/3%, was found to be slightly irritating in eye irritation studies. BPO is considered to irritate the eyes and skin according to the reference data submitted, which are published documents on BPO describing the results of eye irritation studies, primary skin irritation studies, and cumulative irritation studies in rabbits.[86),112),113)]

Eye irritation study of CLDM/BPO Gel, 1%/3%, in rabbits (1549-002)

In an eye irritation study in male NZW rabbits (n = 3/group), 0.1 mL of CLDM/BPO Gel, 1%/3%, or gel base was instilled into the eye,[114)] and eye irritation was evaluated at 1, 24, 48, and 72 hours after

---

[108)] Tanimura A, Specifications and standards for food additives, eighth ed. 2007

[109)] Song S, et al. *J Toxicol Pub Health.* 2003;19(2):123-131

[110)] In the testicles, degenerated spermatids, apoptosis, cell swelling, and multinucleated giant cells were observed. Reduced number of sperms was observed in the epididymis. The applicant explained that vitamin E has an important role in the maintenance and survival of spermatids and in the structural differentiation of principal cells in the epididymis (Mason KE, *Am J Anat.* 1993;52:153-239, Bensoussan K, et al. *J Androl.* 1998;19:266-288) and that BPO might have led decreased vitamin E content in feeds and thereby caused these changes, although this hypothesis has not been confirmed by feed analysis.

[111)] Federal Register. 1982;47(56):p.12444

[112)] Lorenzetti OJ, et al. *J Soc Cosmet Chem.* 1977;28:533-549

[113)] Haustein UF, et al. *Contact Dermatis.* 1985;13:252-257

[114)] Two groups were set for each substance. In one group of animals, eyes were rinsed for 1 minute approximately 1 minute after administration, and in another group of animals, eyes were not rinsed.

administration by the Draize test. Single administration of CLDM/BPO Gel, 1%/3%, or gel base caused mild redness of the conjunctiva, which disappeared by 48 hours after administration, with or without rinsing. CLDM/BPO Gel, 1%/3%, and the gel base caused a similar degree of irritation. Consequently, CLDM/BPO Gel, 1%/3%, was considered to be slightly irritating to the eyes.

3.(iii).A.(7) Other toxicity studies

3.(iii).A.(7).1) Skin sensitization studies (4.2.3.7.2: Reference data: Haustein, 1985[113]; Kimber, 1998[115])

No skin sensitization studies of CLDM/BPO Gel, 1%/3%, were conducted.

The applicant submitted published documents that describe the results of skin sensitization studies of BPO in guinea pigs and mice,[113),115)] and explained that BPO may sensitize the skin.

Skin sensitization study of BPO in mice (Reference data; Kimber, 1998[115])

Female CBA/Ca or CBA/JHsd mice (n = 5/group) received topical application of 25 μL of 0% (acetone), 0.5%, 1%, 2.5%, 5%, or 10% BPO solution to both auricles for 3 days. Five days after the first dose, phosphate buffered saline containing [^{3}H]-methylthymidine or [^{125}I]-isododexyurine was administered via the tail vein, and radioactivity in the auricular lymph nodes was determined. Because the radioactivity levels in the ≥0.5% groups were ≥3 times the control level, BPO was considered to have a skin sensitization potential.

3.(iii).A.(7).2) Photocarcinogenicity studies (4.2.3.7.7: 5619-003: Reference data; Lerche, 2010[116])

In a photocarcinogenicity study of 10% BPO gel in hairless mice, it was determined not to be photocarcinogenic. In a photocarcinogenicity study of CLDM/BPO gel, 1%/5%, in hairless mice, it was determined to be photocarcinogenic.

(a) Photocarcinogenicity studies of BPO (Reference data; Lerche, 2010[116])

BPO (0 [no treatment] or 25 μL of 10% gel) was applied to hairless female C3.Cg/TifBomTac-immunocompetent mice (n = 25/group) nonoccluded once daily, 5 days a week, for 1 year. Animals were exposed to artificial sunlight (0, 2, 3 or 4 SED[117] of 10.7% UVB). The survival rate was lower in animals receiving BPO and UVR exposure than in control animals receiving UVR exposure and in animals receiving BPO and no UVR exposure. The time to first tumor was not shorter in the BPO-treated groups regardless of UVR exposure level as compared with the control animals. Accordingly, it was determined that 10% BPO gel is not photocarcinogenic.

[115] Kimber I, et al. *J Toxicol Environ Health A.* 1998;53:563-579
[116] Lerche CM, et al. *Exp Dermatol.* 2010;19(4):381-386
[117] Standard erythema dose

(b) Photocarcinogenicity study of CLDM/BPO gel, 1%/5% (5619-003)

SKH1-hrBR hairless mice (n = 36/sex/group) percutaneously received 0 (no treatment), 0 (gel base), 25, or 50 μL of CLDM/BPO gel, 1%/5%, (10/50 or 20/100 mg/kg as CLDM/BPO) once daily, 5 days a week for 40 weeks, and were exposed to UVR (300 or 600 J/m^2).[118)] The incidence of erythema, edema, and desquamation at the application site was higher in animals receiving CLDM/BPO gel, 1%/5%, than in control animals. Among animals exposed to UVR at 600 J/m^2, the time to first tumor was shorter and the number of tumors[119)] was greater in animals in the gel base group than in the no treatment group. Animals treated with CLDM/BPO gel, 1%/5%, and exposed to UVR 600 J/m^2 had shorter time to first tumor, higher TPR,[120)] and greater number of tumors[121)] as compared with those treated with gel base and exposed to UVR 600 J/m^2. Consequently, CLDM/BPO gel, 1%/5%, was determined to be photocarcinogenic.

3.(iii).A.(7).3) Toxicity studies on impurities

Toxicity studies on impurities were not conducted. Safety evaluation was conducted in 5 impurities[122)] for which acceptance criteria had been established at levels greater than the qualification threshold specified in ICH Q3B Guideline. The results confirmed these impurities are of little toxicological concern.

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Carcinogenicity of BPO and CLDM/BPO Gel, 1%/3%

The applicant's explanation:

In some genotoxicity studies of BPO (i.e., the chromosomal aberration assay in human lymphocytes and the DNA damage study in human bronchial epithelial cells), the results suggested that BPO is genotoxic, but they are of little biological significance since no neoplastic lesions were observed in 2-year dermal carcinogenicity studies of BPO in rats and mice. BPO is unlikely to be carcinogenic.

PMDA's view:

The applicant's explanation on a low carcinogenic risk of BPO is acceptable. However, the applicant should explain the carcinogenic risk of external formulations of CLDM/BPO, including CLDM/BPO Gel, 1%/3%, since BPO is considered to be a skin tumor promoter.

The applicant's explanation:

BPO has been suggested to act as a tumor promoter but is unlikely to act as an initiator because CLDM is not genotoxic.[123)]. The results of dermal carcinogenicity studies in mice and rats have shown that BPO

[118)] Animals were exposed to UVR 3 days a week (Monday, Wednesday, and Friday) after treatment, and 2 days a week (Tuesday and Thursday) before treatment. The length of UVR exposure was approximately 1 hour.
[119)] Number of tumors ≥1mm in size found per live animal at Week 50 of treatment.
[120)] On the basis of the UVR dose per week and the median number of weeks to the first tumor ≥1 mm in size, the tumor potency factor was calculated to estimate the biological response.
[121)] Number of tumors ≥1mm in size found per live animal at Week 48 of treatment.
[122)] The 5 impurities are 4 impurities of clindamycin, i.e., GSK-01 (≤[redacted]%), GSK-02 (≤[redacted]%), GSK-03 (≤[redacted]%), and GSK-04 (≤[redacted]%), and an impurity of BPO, i.e., GSK-05 (≤[redacted]%).
[123)] Dalacin T Gel 1% [Pharmaceutical Interview Form]. December 2012.

is also unlikely to act as an initiator. Considering that a promoter needs a coadministered initiator to induce tumors, BPO is unlikely to play a stimulatory role for tumor promotion when used with CLDM. In a rat 2-year dermal carcinogenicity study of CLDM/BPO, 1%/5%, formulation, males in the 2000 mg/kg group showed an increase in the incidence of keratoacanthoma, while females in the same dose group showed no increases in the incidence of tumors.[124)] Additionally, no neoplastic lesions were found in mice, which are considered to have higher skin sensitivity than rats, in the following studies: 2-year dermal carcinogenicity study (0475MS.50.001) of CLDM/BPO gel, 1%/5% (the gel base used in this study is identical to that of CLDM/BPO Gel, 1%/3%,); carcinogenicity studies of different formulations of CLDM/BPO, 1%/5%.[125)] It is, therefore, unlikely that carcinogenicity of CLDM/BPO Gel, 1%/3%, is of concern in routine clinical use.

PMDA concluded that the applicant's explanation on the low carcinogenic risk of BPO in routine clinical use is acceptable.

3.(iii).B.(2) Photocarcinogenicity of CLDM/BPO Gel, 1%/3%

PMDA asked the applicant to describe the mechanism of photocarcinogenicity of CLDM/BPO gel, 1%/5%, to explain why the combination gel was more photocarcinogenic (e.g., a shorter time to first tumor) as compared with the gel base in the photocarcinogenicity study, and to discuss the safety of CLDM/BPO Gel, 1%/3%, in humans.

The applicant’s explanation:

Currently, photocarcinogenicity studies as well as rodent models (hairless animals) available for those studies are not sufficient for the data obtained thereof to be extrapolated to humans, and are thus considered not useful.[126),127)] The Crl:SKH1-hrBR hairless mice used in the photocarcinogenicity study have not been validated so far, and feasibility of extrapolating data obtained in the rodent model to the humans is unclear at present.[128)] Since a relationship between the severity of dermal reactions (erythema, edema, and desquamation) and the induction of skin tumors was observed in the study, skin reactions may contribute to an increase in photocarcinogenicity. However, as described above, it is difficult to clarify the mechanism of photocarcinogenicity of CLDM/BPO Gel, 1%/3%, taking account of scientific findings based on up-to-date research results. The current guidelines on photosafety evaluation of pharmaceuticals[126)] do not recommend photogenotoxicity testing for human pharmaceuticals. Even if a photogenotoxicity study is conducted, the results would be difficult to interpret and extrapolate to humans. The applicant did not investigate a possible involvement of photogenotoxicity in the photocarcinogenisity observed in the study.

[124)] BenzaClin Topical Gel [package insert].US. 2009.
[125)] AKANYA Gel [package insert].US. 2008.
[126)] Photosafety Evaluation of Pharmaceuticals (Notification No. 0521-1 of the Evaluation and Licensing Division, PFSB dated May 21, 2014) corresponding to ICH S10
[127)] Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals [ICH M3(R2)] (Notification No. 0219-4 of the Evaluation and Licensing Division, PFSB dated February 19, 2010)
[128)] CPMP/SWP/398/01, Note for guidance on photosafety testing, EMEA. 2002 (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003353.pdf. Accessed October 2014.)

According to a foreign postmarketing study (as of [redacted] 20[redacted]), more than 30 million people have used CLDM/BPO Gel, 1%/3%, since the market launch of the CLDM/BPO, 1%/5%, product in 1999 and very few episodes (3 patients) of photosensitivity reactions have been reported. Considering the low phototoxic risk in routine clinical use, the results of the photocarcinogenicity study of CLDM/BPO gel, 1%/5%, are considered irrelevant to humans.

PMDA concluded that the applicant's explanation is acceptable, but the applicant should provide the study results to healthcare professionals in clinical settings appropriately.

4. Clinical data

4.(i) Summary of biopharmaceutical studies and associated analytical methods

4.(i).A. Summary of the submitted data

The applicant submitted, as reference data, the results of a foreign bioavailability (BA) study of multiple topical administration of CLDM/BPO Gel, 1%/3%, or CLDM/BPO gel, 1%/5%, containing or not containing methylparaben (MP).[129)]

The concentrations of benzoic acid, hippuric acid, CLDM and clindamycin sulfoxide (CLDMSO) in human plasma and urine were determined by the liquid chromatography-tandem mass spectrometry method.[130)] In this section, the dose and concentration of CLDM are expressed as the amount of clindamycin. Both hydrated and anhydrous forms of CLDM were used in CLDM/BPO Gel, 1%/3%, in these studies, and CLDM/BPO Gel, 1%/3%, in this section represents both.

Foreign bioavailability study (Reference data 5.3.1.1; Study W0261-101, May to June 2010)

Approximately 4 g of CLDM/BPO Gel, 1%/3%, or CLDM/BPO gel, 1%/5%, containing or not containing MP was applied once daily for 5 days to the face, upper chest, upper back, and shoulders of patients with moderate or severe acne vulgaris. The pharmacokinetics of CLDM were analyzed in 72 patients. Table 11 summarizes pharmacokinetic parameters of CLDM in plasma. The applicant explained that the peak plasma concentration (C_{max}) and area under plasma concentration-time curve (AUC) were not affected by BPO.

[129)] A preservative which was then contained in the CLDM/BPO, 1%/5%, product approved outside Japan was found to lead to allergic contact dermatitis; a MP-free product was developed [see "4.(iii).B.(7) Dosage and administration"].

[130)] The lower limits of quantification for tested compounds
Study STF115959; 100 ng/mL for benzoic acid in plasma, 50 ng/mL for hippuric acid in plasma, 0.1 μg/mL for hippuric acid in urine, and 5 μg/mL for hippuric acid in urine.
Study W0261-101; 50 pg/mL for CLDM in plasma, and 50 pg/mL for CLDMSO in plasma.
Study S194-GB-01; 47 pg/mL for CLDM in plasma, 46 pg/mL for CLDMSO in plasma, 47 pg/mL for CLDM in urine, and 46 pg/mL for CLDMSO in urine.

Table 11. Pharmacokinetic parameters of CLDM in plasma after treatment with CLDM/BPO Gel, 1%/3%, or CLDM/BPO gel, 1%/5%, containing or not containing MP applied once daily for 5 days

	No. of patients	Pharmacokinetic parameters [95% CI]			Ratios of PK parameters (CLDM/BPO, 1%/3%:CLDM/BPO, 1%/5%) (%) [90% CI]		
		C_{max} (ng/mL)	AUC_{0-t} (ng·hr/mL)	AUC_{0-tau} (ng·hr/mL)	C_{max}	AUC_{0-t}	AUC_{0-tau}
CLDM/BPO, 1%/3%	24	0.96 [0.68, 1.35]	12.82 [8.92, 18.46]	12.94 [9.07, 18.46]	-	-	-
CLDM/BPO, 1%/5%, with MP	24	1.09 [0.79, 1.53]	15.62 [10.91, 22.37]	16.31[a)] [10.91, 24.37]	87.80 [60.9, 126.6]	82.09 [56.0, 120.3]	79.35 [53.9, 116.9]
CLDM/BPO, 1%/5%, without MP	24	0.81 [0.61, 1.07]	11.40 [8.63, 15.07]	11.43[b)] [8.87, 14.72]	119.12 [82.6, 171.7]	112.45 [76.7, 164.9]	113.25 [77.3, 166.0]

Least squares geometric mean

a) Evaluated in 20 patients, b) Evaluated in 21 patients

4.(i).B Outline of the review by PMDA

PMDA concluded that there are no particular problems with the results of the bioavailability study.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A. Summary of the submitted data

The applicant submitted, as evaluation data, the results of a phase I study of CLDM/BPO Gel, 1%/3%, in patients with acne vulgaris in Japan. The applicant submitted, as reference data, the results of 2 foreign pharmacokinetic studies (including a study submitted as the above-mentioned bioavailability study) in patients with acne vulgaris to whom CLDM/BPO Gel, 1%/3%, CLDM/BPO gel, 1%/5%, or 1% CLDM lotion was applied.

Unless otherwise specified, all pharmacokinetic parameters are expressed as means, and the dose and concentration of CLDM are expressed as those of clindamycin. Both hydrated and anhydrous forms of CLDM were used in CLDM/BPO Gel, 1%/3%, in these studies, and CLDM/BPO Gel, 1%/3%, in this section represents both of them.

4.(ii).A.(1) Japanese phase I study (5.3.3.2; Study STF115959, February to June 2012)

Approximately 0.7 g of CLDM/BPO Gel, 1%/3%, was applied twice daily for 7 days to the entire face (the forehead, nose, cheeks, and chin) of patients with acne vulgaris,[131)] and the pharmacokinetics of benzoic acid and hippuric acid[132)] in plasma and urine were analyzed in 12 patients.[133)] Tables 12 and 13 summarize the results. Plasma benzoic acid concentrations were measurable in 2 of 12 patients. In one of the 2 patients, plasma benzoic acid concentration was measurable only at 1.5 hours after the application on Day 1, and was less than the lower limit of quantification (100 ng/mL) at the other time points. In the other patient, plasma benzoic acid concentrations were measurable at all time points both

131) The gel was applied in the evening on Day 1, in the morning and evening on Days 2 to 7, and in the morning on Day 8.

132) A study of plasma samples spiked with BPO revealed that BPO in the plasma is metabolized into benzoic acid, and is not measurable.

133) Pharmacokinetic parameters were calculated using WinNonlin Ver. 4.1. This software for pharmacokinetic analysis could calculate AUC_{0-last} even when concentration was zero at all time points, or when the slope of the final elimination phase was negative. The software could not calculate AUC_{0-12} when concentrations were zero at all time points, or when the slope of the final elimination phase was negative and the final time point was within 12 hours after administration. C_{max} was calculated as "below the lower detection limit (0)" when plasma concentrations were not detectable all time points after administration.

on Day 1 and after multiple applications (on Day 8). Plasma hippuric acid concentrations were measurable in 8 of 12 patients on Day 1, and 9 of 12 patients on Day 8. Urinary benzoic acid concentrations were measurable in 3 of 12 patients, and urinary hippuric acid concentrations were measurable in all patients.

The applicant explained that plasma benzoic acid concentration was not measurable in most participants at baseline or after the 7-day treatment, and the effects of multiple doses of CLDM/BPO Gel, 1%/3%, on plasma benzoic acid concentrations could not be assessed. The difference in arithmetic mean (90% confidence interval [CI]) pharmacokinetic parameters of plasma hippuric acid concentrations between baseline and after the 7-day treatment was 18.3 [-53.7, 90.3] ng/mL for C_{max}, and 80.0 [-419.1, 579.1] ng·hr/mL for AUC from 0 to last quantifiable concentration time point ($AUC_{0\text{-}last}$). Although the mean differed between baseline and the final time point, the 90% confidence interval was large, and the distribution did not differ between the 2 time points. The applicant explained that multiple applications of CLDM/BPO Gel, 1%/3%, do not affect plasma hippuric acid concentrations.

Table 12. Pharmacokinetic parameters of benzoic acid and hippuric acid in plasma after treatment with CLDM/BPO Gel, 1%/3%, applied twice daily for 7 days

	Time point	Benzoic acid		Hippuric acid	
		No. of patients	Mean ± standard deviation (SD)	No. of patients	Mean ± standard deviation (SD)
C_{max} (ng/mL)	Day 1	12	104.8 ± 329.2	12	94.6 ± 93.9
	Day 8	12	92.0 ± 318.8	12	112.9 ± 110.8
t_{max} (hr)	Day 1	2	1.6, 4.1[a)]	8	0.3 [0, 12.0][b)]
	Day 8	1	6.0[a)]	9	0.5 [0, 12.0][b)]
$AUC_{0\text{-}last}$ (ng·hr/mL)	Day 1	12	1000.7 ± 3457.8	12	669.8 ± 715.0
	Day 8	12	967.9 ± 3353.1	12	749.8 ± 708.8
$AUC_{0\text{-}12}$ (ng·hr/mL)	Day 1	2	56.3, 11960.5[a)]	6	1208.5 ± 593.3
	Day 8	1	11615.3[a)]	9	1049.4 ± 648.3

$AUC_{0\text{-}12}$, Area under time-concentration curve from 0 to 12 hours after application
a) Actual measured values; b) Median [Range]

Table 13. Pharmacokinetic parameters of benzoic acid and hippuric acid in urine after treatment with CLDM/BPO Gel, 1%/3%, applied twice daily for 7 days

	Time point	Benzoic acid		Hippuric acid	
		No. of patients	Mean ± SD	No. of patients	Mean ± SD
$Ae_{0\text{-}12}$ (mg)	Day 1	12	0.004 ± 0.014	12	31.96 ± 21.31
	Day 8	12	0.003 ± 0.009	12	36.70 ± 19.46
$fe_{0\text{-}12}$ (%)	Day 1	-[a)]	-[a)]	-[a)]	-[a)]
	Day 8	12	0.011 ± 0.026	12	114.59 ± 65.12
$fe^*_{0\text{-}12}$ (%)	Day 1	-[a)]	-[a)]	-[a)]	-[a)]
	Day 8	12	- 0.006 ± 0.066	12	7.1 ± 53.11
CL_r (mL/hr)	Day 1	2	0, 0[b)]	8	58,646.5 ± 38,252.1
	Day 8	1	2.5[b)]	9	51,640.0 ± 20,937.0

$Ae_{0\text{-}12}$, Renal excretion from 0 to 12 hours after application; $fe_{0\text{-}12}$, Percentage of benzoic acid or hippuric acid excreted in urine from 0 to 12 hours after application of the dose of BPO;
$fe^*_{0\text{-}12}$, Percentage of benzoic acid or hippuric acid excreted in urine from 0 to 12 hours after application of the dose of BPO ([Excretion on Day 8] - [Excretion on day 1]); CLr, renal clearance
a) $fe_{0\text{-}12}$and $fe^*_{0\text{-}12}$ were calculated after the 7-day treatment (Day 8); b) Actual measured values

4.(ii).A.(2) Foreign phase I study (Reference data 5.3.3.2; Study S194-GB-01, October 1999 to April 2000)

A single dose of 1 g of CLDM/BPO gel, 1%/5%, or 0.5 g of 1% CDLM lotion was applied to the skin of patients with moderate or severe acne vulgaris, and the pharmacokinetics of CLDM in plasma were analyzed in 24 patients (12/group). Table 14 summarizes the results.

Table 14. Pharmacokinetic parameters of CLDM in plasma after a single application of CLDM/BPO gel, 1%/5%, or 1% CLDM lotion

	No. of patients	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-12} (ng·hr/mL)	AUC_{12-24} (ng·hr/mL)
CLDM/BPO gel, 1%/5%, 1 g	12	0.95 ± 0.60	6.3 ± 2.4	6.07 ± 3.44	2.22 ± 1.05
1% CLDM lotion, 0.5 g	12	0.37 ± 0.26	7.0 ± 2.2	2.67 ± 1.89	1.93 ± 1.64

Mean ± SD

AUC_{12-24}, Area under concentration-time curve (AUC) from 12 to 24 hours after application

Multiple doses of 1 g of CLDM/BPO gel, 1%/5%, or 0.5 g of 1% CLDM lotion were applied topically once or twice daily, respectively,[134] for 28 days to patients with moderate or severe acne vulgaris (pharmacokinetics were analyzed in 77 patients: 39 received CLDM/BPO gel, 1%/5%; and 38 received 1% CLDM lotion). Table 15 summarizes CLDM and CLDMSO concentrations in plasma, and Table 16 those in urine.

Table 15. Plasma concentrations of CLDM and CLDMSO in plasma after multiple applications of CLDM/BPO gel, 1%/5%, or 1% CLDM lotion

	CLDM/BPO gel, 1%/5%, 1 g once daily				1% CLDM lotion, 0.5 g twice daily			
	CLDM		CLDMSO		CLDM		CLDMSO	
	No. of patients	Plasma concentration (ng/mL)	No. of patients	Plasma concentration (ng/mL)	No. of patients	Plasma concentration (ng/mL)	No. of patients	Plasma concentration (ng/mL)
Visit 3 - 6 [a] (Days 7 to 28 of treatment)	39	0.44 ± 0.57	39	0.093 ± 0.093	37	0.39 ± 0.40	37	0.077 ± 0.088
Visit 7 (0-96 hours after the final application)	35	0.068 ± 0.223	36	0.013 ± 0.037	30	0.073 ± 0.227	30	0.045 ± 0.051

Mean ± SD

a) Pharmacokinetic parameters were calculated at each time point during Visit 3 to Visit 6 to obtain mean values for each patient, which were summarized to calculate the mean values in each group.

Table 16. Urinary concentrations of CLDM and CLDMSO in urine after multiple applications of CLDM/BPO gel, 1%/5%, or 1% CLDM lotion

	CLDM/BPO gel, 1%/5%, 1 g once daily				1% CLDM lotion, 0.5 g twice daily			
	CLDM		CLDMSO		CLDM		CLDMSO	
	No. of patients	Urinary concentration (ng/mL)	No. of patients	Urinary concentration (ng/mL)	No. of patients	Urinary concentration (ng/mL)	No. of patients	Urinary concentration (ng/mL)
0-12 hours after a single application	11	4.09 ± 3.49	11	0.54 ± 0.41	11	1.62 ± 1.01	11	0.17 ± 0.13
12-24 hours after a single application	12	2.29 ± 1.36	12	0.60 ± 0.28	12	1.71 ± 1.42	12	0.23 ± 0.20
0-24 hours after the final application	28	5.82 ± 10.36	28	5.38 ± 9.08	23	7.83 ± 11.98	23	4.11 ± 3.69

Mean ± SD

4.(ii).B Outline of the review by PMDA

Interactions with other drugs

PMDA asked the applicant to explain the potential drug interactions between BPO and ingredients of other oral and external drugs likely to be used with CLDM/BPO Gel, 1%/3%, in clinical settings.

The applicant's explanation:

Considering the recommendations in the Guidelines for the Treatment of Acne Vulgaris available in Japan,[135] CLDM/BPO Gel, 1%/3%, is expected to be used with oral antimicrobial agents[136] and adapalene, a topical gel.

[134] CLDM/BPO gel, 1%/5%, was applied once daily and 1% CLDM lotion twice daily.

[135] Hayashi N, et al. *The Japanese Journal of Dermatology.* 2008;118:1893-1923

[136] Oral antimicrobial agents listed in the guidelines include minocycline, doxycycline, tetracycline, erythromycin, roxithromycin, clarithromycin, ciprofloxacin, lomefloxacin, tosufloxacin, levofloxacin, faropenem, and cefuroxime axetil.

Benzoic acid, a BPO metabolite found in the skin, is metabolized into hippuric acid in the plasma via glycine conjugation. No reports have indicated that any of the oral antimicrobial drugs likely to be used with CLDM/BPO Gel, 1%/3%, inhibit glycine conjugation. Of these antimicrobial drugs, none of those excreted via the kidney[137] have been reported to block tubular secretion.[138] Nor have any reports indicated that any of these oral antimicrobial drugs affect the decomposition or excretion of BPO. Consequently, these oral antimicrobial drugs are unlikely to affect the decomposition of BPO into benzoic acid or hippuric acid.

In vitro studies have indicated that benzoic acid inhibits OAT1, and hippuric acid inhibits OAT1 and OAT3 with an inhibition constant (K_i) of 30.9, 3.37, and 5.52 μg/mL, respectively. Hippuric acid inhibits CYP3A4, OATP1B1, multidrug resistance-associated protein (MRP) 4, and BCRP with a 50% inhibitory concentration (IC_{50}) of 129 to 241.9, 1202, 177.4, and 657.6 μg/mL, respectively [see "3.(ii).A.(5) Pharmacokinetic drug interactions"]. Since the plasma concentrations of benzoic acid and hippuric acid[139] obtained in Japanese phase I study (Study STF115959) were lower than above mentioned K_i and IC_{50}, it is unlikely that benzoic acid and hippuric acid derived from BPO in CLDM/BPO Gel, 1%/3%, inhibit these transporters or CYP3A4 in routine clinical use.

Consequently, BPO is unlikely to interact with oral antimicrobial drugs that are likely to be used with CLDM/BPO Gel, 1%/3%.

It is also unlikely that BPO in CLDM/BPO Gel, 1%/3%, interacts with adapalene, a topical agent likely to be used with CLDM/BPO Gel, 1%/3%, to cause systemic effects for the following reasons: Adapalene was not detected in the plasma in clinical studies of adapalene in Japanese patients with acne[140]; Adapalene does not inhibit drug-metabolizing enzymes or induce any particular enzymes;[141] and it has not been reported that BPO affects the pharmacokinetic profile of adapalene in patients receiving adapalene/BPO Gel, 0.1%/2.5%.[142] Moreover, it is unlikely that BPO in CLDM/BPO Gel, 1%/3%, interacts with adapalene locally when these drugs are applied to the skin at the same time for the following reasons: in a study on stability of adapalene and BPO in mixed formulations, adapalene did not decompose in the presence of BPO;[143] no reports have suggested that adapalene affects BPO in its absorption through the skin or decomposition in the skin tissues; foreign package inserts for adapalene external formulations or adapalene/BPO Gel, 0.1%/2.5%, do not describe particular precautions in terms of the concomitant use with BPO-containing products.

---

[137] doxycycline, erythromycin, clarithromycin, roxithromycin, ciprofloxacin, lomefloxacin, tosufloxacin, levofloxacin, faropenem, and cefuroxime axetil

[138] Vibramycin Tablets 50 mg/100 mg [package insert]. 2009, Minomycin Capsules 50 mg/100 mg [package insert]. 2013, Rulid Tablets 150 [package insert]. 2013, Achromycin V Capsules [package insert]. 2013, Erythrocin Tablets 100 mg/200 mg [package insert]. 2013, Ozex Tablets 75/150 [package insert]. 2010, Oracef Tablets 250mg [package insert]. 2009, Lomebact Capsules 100 mg [package insert]. 2012, Farom Tablets 150 mg/200 mg [package insert]. 2013, Ciproxan Tablets 100 mg/200 mg [Pharmaceutical Interview Form]. 2012, Cravit Tablets 250 mg/500 mg [package insert]. 2013, Klaricid Tablets 200 mg [package insert]. 2013

[139] Plasma benzoic acid concentrations were measurable in 2 of 12 patients, and the highest concentration was 1.10 μg/mL. Plasma benzoic acid concentrations were below the lower limit of quantification (100 ng/mL) in other patients. The highest plasma hippuric acid concentration observed in this study was 0.343 μg/mL [see "4.(iii).A.(1) Japanese phase I study"].

[140] Differin Gel 0.1% [package insert]. 2013

[141] Differin Gel [Pharmaceutical Interview Form]. 2013

[142] Epiduo [package insert]. UK. 2014

[143] Martin B, et al. *Bri J Dermatol.* 1998;139:8-11

PMDA's view:

No clinical study data are available on the interactions between BPO and drugs likely to be used with CLDM/BPO Gel, 1%/3%. However, no reports have indicated that oral antimicrobial drugs likely to be used with CLDM/BPO Gel, 1%/3%, affect the decomposition or excretion of BPO-related substances (benzoic acid and hippuric acid). Also, since BPO-related substances distribute to plasma only to a limited extent when CLDM/BPO Gel, 1%/3%, applied to the skin, the inhibition of transporters or CYP isoenzymes, which was observed in *in vitro* studies, is unlikely to occur in the body. PMDA concluded that it is unlikely that clinically significant interactions occur between BPO and oral antimicrobial drugs that are likely to be used with CLDM/BPO Gel, 1%/3%. PMDA also concluded that it is unlikely that systemic or local interactions occur between BPO and adapalene because adapalene distributes to the plasma only to a limited extent, and BPO does not affect the pharmacokinetic profile of adapalene when the 2 drugs are used concomitantly; and there is no incompatibility between adapalene and BPO. However, no sufficient data have been accumulated on the interactions between BPO and other drugs. After the market launch, the applicant should collect data on the safety in combination with other drugs, and provide information to healthcare professionals in clinical settings when new findings become available.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A. Summary of the submitted data

The applicant submitted, as evaluation data on the efficacy and safety of CLDM/BPO Gel, 1%/3%, the results of 4 clinical studies: a Japanese phase I study, 2 Japanese phase III studies, and a foreign phase II study. The applicant also submitted, as reference data, the results of a foreign phase III study. Table 17 outlines the clinical studies on the efficacy and safety of CLDM/BPO Gel, 1%/3%. Both hydrated and anhydrous forms of CLDM were used in CLDM/BPO Gel, 1%/3%, in these studies. CLDM/BPO Gel, 1%/3%, in this section represents both.

Table 17. Outlines of clinical studies on the efficacy and safety of CLDM/BPO topical formulations

	Phase	Study	Participants	Major objectives	No. of participants	Dosage regimen
Evaluation data						
Japan	I	STF114849	Healthy adult volunteers	Safety	20	Using Finn Chamber, patches containing CLDM/BPO Gel, 1%/3%, 3% BPO gel, 5% BPO gel, gel base, or distilled water, and a blank patch were applied to the skin once, or once daily for 7 days by the closed method
	III	STF115287	Patients with acne vulgaris	Efficacy Safety	204	CLDM/BPO Gel, 1%/3%, once daily, 12 weeks
					296	CLDM/BPO Gel, 1%/3%, twice daily, 12 weeks
					299	1% CLDM gel, twice daily, 12 weeks
	III	STF115288	Patients with acne vulgaris	Efficacy Safety	178	3% BPO gel, once daily, 12 weeks
					182	Gel base, once daily, 12 weeks
Outside Japan	II	159	Patients with acne vulgaris	Efficacy Safety	66	CLDM/BPO gel, 1%/5%, once daily, 12 weeks
					63	CLDM/BPO gel, 1%/4%, once daily, 12 weeks
					65	CLDM/BPO gel, 1%2%, once daily, 12 weeks
					64	Gel base, once daily, 12 weeks
Reference data						
Outside Japan	III	W0261-301	Patients with acne vulgaris	Efficacy Safety	327	CLDM/BPO Gel, 1%/3%, once daily, 12 weeks
					328	1% CLDM, once daily, 12 weeks
					328	3% BPO gel, once daily, 12 weeks
					332	Gel base, once daily, 12 weeks

4.(iii).A.(1) Japanese phase I study (5.3.5.4: Study STF114849; November 2010 to February 2011)

A randomized, single-blind comparative study was conducted in healthy adult Japanese volunteers at a medical institution in Japan with a target sample size of 20 (10/sex) to investigate the safety of single and multiple applications of CLDM/BPO Gel, 1%/3%.

Five patches, each containing CLDM/BPO Gel, 1%/3%, 3% BPO gel, 5% BPO gel, gel base, or distilled water, and a blank patch were applied to the skin occluded with Finn Chamber once only, or once daily for 7 days. Two sets of 6 patches were applied to the right and left of upper back, with one set for simple patch test and the other set for photo-patch test.[144] In the single-application, the 6 patches for the simple patch test were applied for 48 hours to assess for skin irritation reactions, and those for the photo-patch test[145] were applied for 24 hours to assess for phototoxicity[146] and photoallergic reactions.[147] In the multiple applications, the patches were applied to the skin for 23 hours a day. Skin reactions at the patch site were observed and rated according to criteria for patch test reading.[148]

[144] Gel patches containing study gel were applied to the skin on Day 1 to conduct a single application test. From Day 5 onward, the same set of patches were applied once daily in the morning for 7 days.

[145] Evaluation of phototoxicity: The patch was removed at 24 hours after the initiation of application in the single application study and at 24 hours after the initiation of last application in the multiple application study, and the application site was exposed with UVA at 6.0 J/cm^2. The application site was observed for skin reactions at 30 minutes after the exposure.
Evaluation of photoallergy: After the evaluation of phototoxicity, the exposed and non-exposed application sites were covered with blank patches, and protected from light for approximately 24 hours. In order to assess the presence/absence of photoallergic reactions, skin reactions immediately before the single application or the first application of the study and at 24 and 48 hours after UVA exposure (approximately 48 and 72 hours after starting the patch application) were compared with non-exposed reference sites in the same participant.

[146] Phototoxicity is defined as acute tissue reactions caused by substances that develop as a result of exposure to light

[147] Photoallergic reaction is defined as an immune response triggered when chemical substances produce photo-reaction products such as protein adducts by photochemical reaction.

[148] Sugai T, *Hifu*. 1977;19(2):210-222

All 20 participants in the patch tests were included in the safety analysis set.

The skin irritation index score[149)] for CLDM/BPO Gel, 1%/3%, was 20.0 after the single application and 65.0 after the multiple applications. CLDM/BPO Gel, 1%/3%, was thus considered to need improvement.[150)] No phototoxicity or photoallergic reactions were observed. The applicant explained that the skin irritation index scores obtained after the multiple applications of 3% BPO gel and 5% BPO gel were both 70.0, which indicate that BPO is a skin irritant and that the multiple occluded applications in this study enhanced the skin irritation caused by CLDM/BPO Gel, 1%/3%.

Adverse events including abnormal laboratory findings (AEs) and adverse drug reactions[151)] including abnormal laboratory findings (ADRs) developed in 65.0% (13 of 20) and 50.0% (10 of 20) of the participants, respectively. AEs that developed in ≥3 participants were application site pruritus observed in 30.0% (6 of 20), erythema in 20.0% (4 of 20), alanine aminotransferase (ALT) increase in 15.0% (3 of 20), and aspartate aminotransferase (AST) increase in 15.0% (3 of 20). These AEs were considered as ADRs.

No deaths, serious adverse events, or adverse events that resulted in the discontinuation of the study were observed.

4.(iii).A.(2) Foreign phase II study (5.3.5.1: Study 159 [March to September 2006])

A randomized, placebo-controlled, double-blind, parallel-group comparative study was conducted in patients with acne vulgaris[152)] at 10 medical institutions in the US to investigate the efficacy and safety of CLDM/BPO gels with a target sample size of 240 (60/group).

CLDM/BPO gel, 1%/5%, 1%/4%, or 1%/2%, or gel base was applied in a thin layer to the entire face of patients once daily at bedtime for 12 weeks.

All 258 patients randomized in the study (66 in the CLDM/BPO, 1%/5%, group; 63 in the CLDM/BPO, 1%/4%, group; 65 in the CLDM/BPO, 1%/2%, group; and 64 in the gel base group) were included in the intention-to-treat (ITT) population for which efficacy was analyzed. A total of 251 patients in whom the study gel (65 in the CLDM/BPO, 1%/5%, group; 63 in the CLDM/BPO, 1%/4%, group; 62 in the CLDM/BPO, 1%/2%, group; and 61 in the gel base group) was actually applied to were included in the safety analysis set.

[149)] The skin irritation index score was calculated using the following formula. Safety of study gel is judged as safe when the score is ≤5.0; acceptable when the score ranges from >5.0 to 15.0; and requires improvement when the score ranges from >15.0 to 30.0. (The sum of the highest score in each participant/Number of participants analyzed) × 100

[150)] The skin irritation index score after the multiple applications of CLDM/BPO Gel, 1%/3%, was 65.0, higher than the upper limit of the score range (30.0) for "requires improvement." However, CLDM/BPO Gel, 1%/3%, was determined to be classified as "requires improvement."

[151)] ADRs are defined as AEs that are considered by the investigator or subinvestigator to be "reasonably possibly" related to the application of the study gel.

[152)] Participants were patients aged 12 to 40 years who have 20 to 55 inflammatory lesions, 12 to 150 non-inflammatory lesions, and ≤3 nodules or cysts on the face.

Table 18 summarizes the changes in the number of inflammatory and non-inflammatory lesions from baseline to Week 12, which was the primary endpoint. Table 19 summarizes the percentage of patients achieving ≥2-point improvement in Investigator's Global Assessment (IGA) score[153] from baseline to Week 12 in the ITT population.

Table 18. Changes in number of inflammatory and non-inflammatory lesions from baseline to Week 12 (ITT population)

	CLDM/BPO, 1%/5%	CLDM/BPO, 1%/4%	CLDM/BPO, 1%/2%	Gel base
inflammatory lesions				
Baseline	27.3 ± 8.65 (66)	25.6 ± 6.92 (63)	26.5 ± 7.07 (65)	26.5 ± 8.05 (64)
Week 12 of treatment	12.2 ± 10.16 (65)	9.4 ± 7.50 (63)	8.9 ± 6.88 (61)	17.0 ± 13.56 (61)
Change	-15.3 ± 9.92 (65)	-16.2 ± 9.13 (63)	-17.7 ± 7.89 (61)	-9.7 ± 12.97 (61)
Between-group difference with gel base [95% CI] a)	4.99 [1.91, 8.08]	6.98 [3.87, 10.09]	7.77 [4.63, 10.90]	-
P value a)b)	$P = 0.002$	$P < 0.001$	$P < 0.001$	-
Non-inflammatory lesions				
Baseline	39.8 ± 25.42 (66)	31.0 ± 17.56 (63)	36.6 ± 22.14 (65)	33.6 ± 15.39 (64)
Week 12 of treatment	23.0 ± 20.77 (65)	20.8 ± 18.82 (63)	22.8 ± 18.22 (61)	26.1 ± 18.54 (61)
Change	-17.1 ± 17.58 (65)	-10.3 ± 12.86(63)	-12.1 ± 16.64 (61)	-7.4 ± 15.85 (61)
Between-group difference with gel base [95% CI] a)	7.53 [2.65, 12.41]	3.81 [-1.07, 8.58]	4.02 [-0.91, 8.94]	-
P value a)b)	$P = 0.003$	$P = 0.125$	$P = 0.110$	-

Mean ± SD (No. of patients)
a) A model of analysis of covariance (ANCOVA) with group, baseline value, and medical institution as explanatory variables
b) The step-down method, where pairwise comparisons were ranked from the CLDM/BPO, 1%/5%, group vs. the gel base group, the CLDM/BPO, 1%/4%, group vs. the gel base group, to the CLDM/BPO, 1%/2% group vs. the gel base group, was used to adjust for multiplicity with a two-tailed level of significance of 0.0167 (these analytical results were obtained according to the analysis plan in the statistical analysis plan).

Table 19. Percentage of participants achieving ≥2-point improvement in IGA score from baseline to Week 12 (ITT population)

	CLDM/BPO, 1%/5%	CLDM/BPO, 1%/4%	CLDM/BPO, 1%/2%	Gel base
Percentage of participants with ≥2-point improvement in IGA score from baseline	34.9% (23/66)	33.3% (21/63)	30.8% (20/65)	14.1% (9/64)
P value a)b)	$P = 0.007$	$P = 0.010$	$P = 0.024$	-

No. of patients (%)
a) The Cochran-Mantel-Haenszel test stratified by medical institutions
b) The step-down method where pairwise comparisons were ranked from the CLDM/BPO, 1%/5%, group vs. the gel base group, the CLDM/BPO, 1%/4%, group vs. the gel base group, to the CLDM/BPO, 1%/2%, group vs. the gel base group was used to adjust for multiplicity with a two-tailed level of significance of 0.0167 (these analytical results were obtained according to the analysis plan in the statistical analysis plan).

AEs developed in 24.6% (16 of 65) of patients in the CLDM/BPO, 1%/5%, group; 34.9% (22 of 63) of patients in the CLDM/BPO, 1%/4%, group; 17.7% (11 of 62) of patients in the CLDM/BPO, 1%/2%, group; and 24.6% (15 of 61) of patients in the gel base group. ADRs[154] developed in 12.3% (8 of 65) of patients in the CLDM/BPO, 1%/5%, group; 22.2% (14 of 63) of patients in the CLDM/BPO, 1%/4%, group; 8.1% (5 of 62) of patients in the CLDM/BPO, 1%/2%, group; and 14.8% (9 of 61) of patients in the gel base group. Table 20 summarizes AEs and ADRs observed in ≥2% of patients in any group.

[153] At Weeks 0, 3, 6, 9, and 12 of treatment, the investigator assessed the overall severity of acne vulgaris, and rated using the following scale: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe; and 5 = worsened.
[154] ADRs were defined as AEs for which a causal relationship to the study gel was rated as "possibly related," "probably related," or "definitely related" by the investigator.

Table 20. Adverse events and adverse drug reactions reported by ≥2% of patients in any group (safety analysis set)

Adverse events	Adverse events				Adverse drug reactions			
	CLDM /BPO, 1%/5%	CLDM /BPO, 1%/4%	CLDM /BPO, 1%/2%	Gel base	CLDM /BPO, 1%/5%	CLDM /BPO, 1%/4%	CLDM /BPO, 1%/2%	Gel base
No. of patients	65	63	62	61	65	63	62	61
Overall	16 (24.6)	22 (34.9)	11 (17.7)	15 (24.6)	8 (12.3)	14 (22.2)	5 (8.1)	9 (14.8)
Application site dryness	3 (4.6)	3 (4.8)	1 (1.6)	2 (3.3)	3 (4.6)	3 (4.8)	1 (1.6)	2 (3.3)
Application site irritation	1 (1.5)	5 (7.9)	0	1 (1.6)	1 (1.5)	5 (7.9)	0	1 (1.6)
Application site erythema	0	1 (1.6)	0	2 (3.3)	0	1 (1.6)	0	2 (3.3)
Upper respiratory tract infection	1 (1.5)	4 (6.3)	0	0	0	0	0	0
Dry skin	2 (3.1)	1 (1.6)	1 (1.6)	0	2 (3.1)	1 (1.6)	1 (1.6)	0
Acne	0	1 (1.6)	0	2 (3.3)	0	1 (1.6)	0	2 (3.3)
Skin burning sensation	0	2 (3.2)	1 (1.6)	1 (1.6)	0	2 (3.2)	1 (1.6)	1 (1.6)
Erythema	0	0	2 (3.2)	1 (1.6)	0	0	2 (3.2)	1 (1.6)
Skin exfoliation	2 (3.1)	0	1 (1.6)	0	2 (3.1)	0	1 (1.6)	0
Oropharyngeal pain	1 (1.5)	0	0	2 (3.3)	0	0	0	0

No. of patients (%)

No deaths occurred during the study. A serious AE (forearm fracture) developed in 1 patient in the CLDM/BPO, 1%/2%, group. A causal relationship to the study gel was ruled out. The outcome was "recovered/resolved." Three patients discontinued treatment due to AEs [hypersensitivity in 1 patient in the CLDM/BPO, 1%/2%, group; acne and rash in 1 patient each in the CLDM/BPO, 1%/4%, group; acne, erythema, skin burning sensation, and swelling face in 1 patient each in the gel base group (some patients experienced more than one event)]. A causal relationship to the study gel was not ruled out for any of these events. The outcome was "recovered/resolved" in all cases except one case of acne, which was unchanged.

4.(iii).A.(3) Phase III studies

4.(iii).A.(3).1) Japanese phase III study (5.3.5.1: Study STF115287; September 2011 to August 2012)

A randomized, single-blind,[155] parallel-group comparative study was conducted in patients with acne vulgaris[156] at 26 medical institutions in Japan to investigate the efficacy and safety of once-daily or twice-daily topical application of CLDM/BPO Gel, 1%/3%, vs. CLDM as control with a target sample size of 800 (200 in CLDM/BPO Gel, 1%/3%, once-daily treatment group, and 300 each in CLDM/BPO Gel, 1%/3%, twice-daily treatment group and the 1% CLDM twice-daily treatment group).

An appropriate amount[157] of CLDM/BPO Gel, 1%/3%, was applied once daily at bedtime or twice daily in the morning and evening (or at bedtime), or an appropriate amount of 1% CLDM gel was applied twice daily in the morning and at bedtime to the entire face (including the forehead, nose, cheeks, and chin) of patients for 12 weeks.

[155] As the dosing interval and dose appearance differ between study gels, a double-blind comparison was not feasible. Accordingly, investigators or subinvestigators assessed clinical findings during the study in an assessor-blinded manner (not knowing patient allocation).
[156] Participants were patients aged 12 to 45 years who have 17 to 60 inflammatory lesions (red papules and pustules) and 20 to 150 non-inflammatory lesions (open and closed comedones) on the face. Patients with cysts or nodules were excluded.
[157] Each time of application, 2 fingertip units (FTUs, the tip of the index finger) of the study gel was to be applied.

The primary endpoint was the change in the total number of lesions from baseline to Week 12. The purpose of the study was to demonstrate the superiority of twice-daily applications of CLDM/BPO Gel, 1%/3%, over twice-daily applications of 1% CLDM gel in the ITT population, and the non-inferiority of once-daily application of CLDM/BPO Gel, 1%/3%, over twice-daily application of 1% CLDM gel in the per-protocol set (PPS).

Of 800 patients randomized for the study, 799 patients (204 in the CLDM/BPO Gel, 1%/3%, once-daily group; 296 in the CLDM/BPO Gel, 1%/3%, twice-daily group; 299 in the 1% CLDM twice-daily group) were included in the ITT population, and were assessed for safety. Excluded was 1 patient (consent withdrawal) in whom the study gel was not applied to. Of the ITT population, 706 patients were included in the PPS (177 in the CLDM/BPO Gel, 1%/3%, once-daily treatment group; 249 in the CLDM/BPO Gel, 1%/3%, twice-daily treatment group; 280 in the 1% CLDM twice-daily group) after excluding 93 patients who substantially violated the protocol.[158)]

Table 21 summarizes the change in the total number of lesions from baseline to Week 12 (the primary endpoint) in the ITT population. A pairwise comparison between the CLDM/BPO, 1%/3%, twice-daily group and the 1% CLDM twice-daily group revealed a statistically significant difference, which demonstrated the superiority of CLDM/BPO, 1%/3%, twice-daily treatment over 1% CLDM gel twice-daily treatment.

Table 21. Change in the total number of lesions from baseline to Week 12 of treatment (ITT population)

	CLDM/BPO, 1%/3%, once-daily	CLDM/BPO, 1%/3%, twice daily	1% CLDM twice daily
Baseline	76.3 ± 30.05 (204)	80.2 ± 36.05 (296)	79.6 ± 37.76 (299)
Week 12 of treatment	20.7 ± 24.35 (201)	19.8 ± 20.73 (289)	30.6 ± 36.22 (299)
Change	-55.1 ± 29.59 (201)	-60.4 ± 34.58 (289)	-48.9 ± 34.92 (299)
Between-group difference with the 1% CLDM twice-daily [95% CI] [a)]	-8.2 [-12.9, -3.6]	-11.0 [-15.0, -7.0]	
P value[a)]	-	$P < 0.001$	

Mean ± SD (No. of patients)
a) A model of analysis of covariance (ANCOVA) with group, baseline value, and medical institution as explanatory variables

As Table 22 shows, a pairwise comparison between the CLDM/BPO, 1%/3%, once-daily group and the 1% CLDM twice-daily group demonstrated non-inferiority of CLDM/BPO, 1%/3%, once-daily treatment over 1% CLDM twice-daily treatment, because the upper limit of the 95% confidence interval for the difference between the 2 groups was lower than the pre-defined non-inferiority margin[159)] of 3.8.

[158)] Common violations of the protocol are "not conducting necessary efficacy evaluation at baseline or Week 12," which was reported by 10.3% (21 of 204) of patients in the CLDM/BPO once-daily group, 11.5% (34 of 296) of patients in the CLDM/BPO twice-daily group, and 3.0% (9 of 299) of patients in the 1% CLDM twice-daily group; and "using prohibited drugs (antimicrobial agents)" by 3.4% (7 of 204) of patients, 3.4% (10 of 296) of patients, and 2.3% (7 of 299) of patients in the corresponding groups.

[159)] As the change in the total number of lesions from baseline to Week 12 was -35.5 in the 1% CLDM once-daily group, and -27.8 in the gel base once-daily group in the foreign phase III study (Study W0261-301), the non-inferiority margin was set at approximately half of the difference between the 2 groups (3.8).

Table 22. Change in the total number of lesions from baseline to Week 12 of treatment (PPS)

	CLDM/BPO, 1%/3%, once daily	CLDM/BPO, 1%/3%, twice daily	1% CLDM twice daily
Baseline	75.6 ± 29.42 (177)	81.0 ± 36.43 (249)	80.5 ± 38.07 (280)
Week 12 of treatment	18.1 ± 17.09 (177)	18.0 ± 19.95 (249)	30.5 ± 35.62 (280)
Change	-57.5 ± 26.72 (177)	-63.0 ± 33.57 (249)	-50.0 ± 34.26 (280)
Between-group difference with the 1% CLDM twice-daily [95% CI] [a)]	-10.3 [-14.8, -5.7]		

Mean ± SD (No. of patients)
a) A model of analysis of covariance (ANCOVA) with group, baseline value, and medical institution as explanatory variables

AEs were reported in 52.9% (108 of 204) of patients in the CLDM/BPO once-daily group; in 55.1% (163 of 296) of patients in the CLDM/BPO twice-daily group; and in 36.8% (110 of 299) of patients in the 1% CLDM twice-daily group. ADRs[151)] were reported in 24.0% (49 of 204) of patients in the CLDM/BPO once-daily group; in 35.1% (104 of 296) of patients in the CLDM/BPO twice-daily group; and in 9.0% (27 of 299) of patients in the 1% CLDM twice-daily group. Table 23 summarizes AEs and ADRs observed in ≥2% of patients in any group.

Table 23. Adverse events and adverse drug reactions reported by ≥2% of participants in any group (ITT population)

Adverse events	Adverse events			Adverse drug reactions		
	CLDM/BPO, 1%3%, once daily	CLDM/BPO, 1%/3%, twice daily	1% CLDM twice daily	CLDM/BPO, 1%/3%, once daily	CLDM/BPO, 1%3%, twice daily	1% CLDM twice daily
No. of patients	204	296	299	204	296	299
All events	108 (52.9)	163 (55.1)	110 (36.8)	49 (24.0)	104 (35.1)	27 (9.0)
Dry skin	17 (8.3)	35 (11.8)	8 (2.7)	15 (7.4)	34 (11.5)	6 (2.0)
Dermatitis contact	14 (6.9)	24 (8.1)	5 (1.7)	11 (5.4)	23 (7.8)	3 (1.0)
Erythema	8 (3.9)	22 (7.4)	8 (2.7)	8 (3.9)	21 (7.1)	8 (2.7)
Pruritus	9 (4.4)	17 (5.7)	6 (2.0)	9 (4.4)	17 (5.7)	6 (2.0)
Skin exfoliation	4 (2.0)	25 (8.4)	2 (0.7)	4 (2.0)	25 (8.4)	2 (0.7)
Eczema	4 (2.0)	10 (3.4)	7 (2.3)	1 (0.5)	5 (1.7)	0
Dermatitis exfoliative	4 (2.0)	6 (2.0)	4 (1.3)	4 (2.0)	6 (2.0)	4 (1.3)
Skin irritation	3 (1.5)	8 (2.7)	2 (0.7)	3 (1.5)	8 (2.7)	2 (0.7)
Nasopharyngitis	28 (13.7)	48 (16.2)	39 (13.0)	0	0	0
Influenza	4 (2.0)	9 (3.0)	7 (2.3)	0	0	0
Burning sensation	6 (2.9)	12 (4.1)	4 (1.3)	6 (2.9)	12 (4.1)	4 (1.3)
Facial pain	9 (4.4)	9 (3.0)	4 (1.3)	9 (4.4)	9 (3.0)	4 (1.3)

No. of patients (%)

No deaths or serious adverse events developed. AEs leading to treatment discontinuation were observed in a total of 51 patients, which included dermatitis contact in 8 patients, erythema and eczema in 2 patients each, and urticaria, dry skin, dermatitis exfoliative, pruritus, seborrhoeic dermatitis, swollen face, eyelid oedema, pneumonia mycoplasmal, and facial pain in 1 patient each in the CLDM/BPO once-daily treatment group; dermatitis contact in 16 patients, erythema in 3 patients, eczema and urticaria in 2 patients each, and dry skin, skin irritation, skin exfoliation, eyelid oedema, upper respiratory tract infection, and burning sensation in 1 patient each in the CLDM/BPO twice-daily treatment group; and dermatitis contact in 2 patients, and skin irritation, acne, asteatosis, rash maculo-papular, burning sensation, ALT increased, AST increased, blood alkaline phosphatase increased, blood lactate dehydrogenase (LDH) increased, and gamma-glutamyltransferase (γ-GTP) increased in 1 patient each

in the 1% CLDM twice-daily group (some patients discontinued treatment due to more than one AE). A causal relationship to the treatment was ruled out for seborrhoeic dermatitis, eczema,[160] pneumonia mycoplasmal, unicaria,[160] upper respiratory tract infection, rash maculo-papular, ALT increased, AST increased, blood alkaline phosphatase increased, blood LDH increased, γ-GTP increased, acne, and asteatosis; and was not ruled out for other AEs. The outcome was "recovered/resolved" in all AEs other than asteatosis (the outcome was "not changed"), and γ-GTP increased (the outcome was "recovering/resolving").

4.(iii).A.(3).2) Japanese phase III study (5.3.5.1; Study STF115288, July 2011 to April 2012)

Since BPO is a new active ingredient in Japan, a randomized, placebo-controlled, double-blind, parallel comparative study was conducted in patients with acne vulgaris[161] at 19 medical institutions in Japan to evaluate the efficacy and safety of 3% BPO gel with a target sample size of 360 (180/group).

An appropriate amount[157] of 3% BPO gel, or gel base was applied once daily at bedtime to the entire face (including the forehead, nose, cheeks, and chin) of patients for 12 weeks.

All 360 patients randomized (178 in the 3% BPO group, 182 in the gel base group) in whom the study gel was actually applied were included in the ITT population for whom the efficacy and safety of the study gel were analyzed.

Table 24 summarizes the change in the total number of lesions from baseline to Week 12 (the primary endpoint) in the ITT population. A pairwise comparison between the 3% BPO group and the gel base group revealed a statistically significant difference, which demonstrated the superiority of 3% BPO over the gel base.

Table 24. Change in the total number of lesions from baseline to Week 12 of treatment (ITT population)

	3% BPO	Gel base
Baseline	72.1 ± 33.40 (178)	70.3 ± 30.89 (182)
Week 12 of treatment	28.2 ± 24.74 (177)	48.1 ± 36.14 (182)
Change	-44.0 ± 32.34 (177)	-22.2 ± 34.02 (182)
Between-group difference [95% CI][a)]	-21.0 [-26.2, -15.8]	
P value[a)]	$P < 0.001$	

Mean ± SD (No. of patients)

a) A model of analysis of covariance (ANCOVA) with group, baseline value, and medical institution as explanatory variables

AEs were observed in 57.9% (103 of 178) of patients in the 3% BPO group, and in 47.3% (86 of 182) of patients in the gel base group. ADRs[151] were observed in 30.3% (54 of 178) of patients in the 3% BPO group, and in 5.5% (10 of 182) of patients in the gel base group. Table 25 summarizes AEs and ADRs observed in ≥2% of patients in any group.

[160] For eczema and urticaria, a causal relationship between the AE and treatment was not ruled out in any cases other than those observed in the CLDM/BPO, 1%/3%, once-daily treatment group.

[161] Participants were patients aged 12 to 45 years who have 17 to 60 inflammatory lesions (red papules and pustules) and 20 to 150 non-inflammatory lesions (open and closed comedones) on the face. Patients with cysts or nodules were excluded.

Table 25. Adverse events and adverse drug reactions reported by ≥2% of participants in any group (ITT population)

Adverse events	Adverse events		Adverse drug reactions	
	3% BPO	Gel base	3% BPO	Gel base
No. of patients	178	182	178	182
Overall	103 (57.9)	86 (47.3)	54 (30.3)	10 (5.5)
Nasopharyngitis	40 (22.5)	53 (29.1)	0	0
Influenza	5 (2.8)	2 (1.1)	0	0
Dry skin	16 (9.0)	6 (3.3)	14 (7.9)	2 (1.1)
Dermatitis contact	16 (9.0)	2 (1.1)	12 (6.7)	1 (0.5)
Pruritus	13 (7.3)	4 (2.2)	13 (7.3)	4 (2.2)
Erythema	10 (5.6)	2 (1.1)	9 (5.1)	2 (1.1)
Skin irritation	7 (3.9)	1 (0.5)	6 (3.4)	0
Facial pain	19 (10.7)	2 (1.1)	18 (10.1)	2 (1.1)
Headache	4 (2.2)	1 (0.5)	0	0

No. of patients (%)

No deaths or serious adverse events developed. AEs leading to treatment discontinuation were observed in 17 patients (dermatitis contact in 7 patients, erythema in 3 patients, pruritus in 2 patients, dry skin, skin exfoliation, skin irritation, facial pain, and frostbite in 1 patient each in the 3% BPO group; and dermatitis contact, pruritus, dry skin, acne, eczema, eczema asteatotic, and facial pain in 1 patient each in the gel base group (some patients experienced more than one AE)]. A causal relationship to the study gel was ruled out for frostbite, acne, and eczema, but not for the other events. The outcome was "recovering/resolving" or "recovered/resolved" in all events.

4.(iii).A.(3).3) Foreign phase III study (Reference data 5.3.5.1; Study W0261CD-301, October 2008 to September 2009)

A randomized, double-blind, parallel-group comparative study was conducted in patients with acne vulgaris[162)] at 24 medical institutions in the US, Canada, and other counties to investigate the efficacy and safety of CLDM/BPO Gel, 1%/3%, vs. CLDM and placebo as controls with a target sample size of 1320 (330/group).

An appropriate amount[157)] of CLDM/BPO Gel, 1%/3%, 1% CLDM gel, 3% BPO gel, or gel base was applied once daily in the morning or evening to the entire face (including the forehead, nose, cheeks, and chin) of patients for 12 weeks.

The purpose of the study is to demonstrate statistically significant differences in all pairwise comparisons between CLDM/BPO Gel, 1%/3%, group and the 3 control groups (the 1% CLDM, 3% BPO, gel base groups) in terms of "the changes in 2 kinds of eruption count of the following 3 different eruption counts (i.e., inflammatory, non-inflammatory, and total lesion counts)" and "percentage of patients achieving ≥2-point improvement in ISGA[163)] score from baseline to Week 12."

[162)] Participants were patients aged 12 to 45 years who have 17 to 60 inflammatory lesions (red papules and pustules) and 20 to 150 non-inflammatory lesions (open and closed comedones) on the face. Patients with cysts or nodules were excluded.

[163)] At Weeks 0, 2, 4, 8, and 12 of treatment, the investigator assessed the overall severity of acne vulgaris, and rated using the following scale: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe; and 5 = very severe.

Of 1319 patients randomized for the study, 1315 patients (327 in the CLDM/BPO, 1%/3%, group; 328 in the 1% CLDM group; 328 in the 3% BPO group; and 332 in the gel base group) were included in the ITT population to be evaluated for efficacy and safety. Excluded were 4 patients (loss to follow-up or consent withdrawal) in whom the study gel was not applied to.

Tables 26 and 27 summarize the percentage of patients achieving ≥2-point improvement in ISGA score from baseline to Week 12 in the ITT population, and the changes in the numbers of inflammatory, non-inflammatory, and total lesions from baseline to Week 12 in the ITT population, respectively, which were the primary endpoints. In pairwise comparisons between CLDM/BPO Gel, 1%/3%, and the control groups in the changes in the numbers of lesions from baseline to Week 12, statistically significant differences were observed in the numbers of 2 of the 3 different lesions. The pairwise comparisons between the CLDM/BPO Gel, 1%/3%, group and the 3 control groups revealed that the percentage of patients achieving ≥2-point improvement in ISGA score from baseline to Week 12 was, statistically, significantly higher in CLDM/BPO Gel, 1%/3%, group.

Table 26. Percentage of participants with a ≥2-point improvement in ISGA score at Week 12 from baseline (ITT population)

	CLDM/BPO, 1%/3%	1% CLDM	3% BPO	Gel base
Percentage of patients achieving ≥2-point improvement in ISGA score from baseline to Week 12	39.4% (129/327)	25.0% (82/328)	30.5% (100/328)	17.8% (59/332)
P value[a)]	-	$P < 0.001$	$P = 0.016$	$P < 0.001$

No. of patients (%)
a) The Cochran-Mantel-Haenszel test stratified by medical institutions

Table 27. Changes in the numbers of inflammatory, non-inflammatory, and total lesions from baseline to Week 12 of treatment (ITT population)

	CLDM/BPO, 1%/3%	1% CLDM	3% BPO	Gel base
No. of inflammatory lesions				
Baseline	26.6 ± 9.2 (327)	26.7 ± 9.6 (328)	27.0 ± 10.4 (328)	26.3 ± 9.8 (332)
Week 12 of treatment	8.3 ± 8.5 (322)	11.2 ± 10.9(318)	10.2 ± 9.5(323)	13.2 ± 11.0 (329)
Change	-18.2 ± 10.4 (322)	-15.6 ± 11.6 (318)	-16.8 ± 11.5 (323)	-13.1 ± 12.1 (329)
Between-group difference [95% CI][a)]	-	-2.68 [-3.97, -1.39]	-1.59 [-2.86, -0.32]	-4.89 [-6.16, -3.62]
P value[a)]	-	$P < 0.001$	$P = 0.015$	$P < 0.001$
No. of non-inflammatory lesions				
Baseline	46.1 ± 25.6 (327)	46.4 ± 26.1 (328)	44.6 ± 23.8 (328)	44.2 ± 24.4 (332)
Week 12 of treatment	21.1 ± 18.5 (322)	26.1 ± 22.2 (318)	22.6 ± 20.3 (323)	29.1 ± 25.9 (329)
Change	-24.8 ± 20.1 (322)	-19.8 ± 19.8 (318)	-22.2 ± 17.6 (323)	-14.8 ± 21.6 (329)
Between-group difference [95% CI][a)]	-	-4.90 [-7.37, -2.43]	-2.06 [-4.53, 0.41]	-9.48 [-11.93, -7.03]
P value[a)]	-	$P < 0.001$	$P = 0.102$	$P < 0.001$
Total number of lesions				
Baseline	72.7 ± 30.4 (327)	73.1 ± 31.6 (328)	71.6 ± 29.8 (328)	70.5 ± 29.7 (332)
Week 12 of treatment	29.4 ± 23.9 (322)	37.3 ± 29.4 (318)	32.8 ± 26.5 (323)	42.3 ± 33.4 (329)
Change	-43.0 ± 27.1 (322)	-35.5 ± 27.1 (318)	-39.0 ± 25.0 (323)	-27.8 ± 29.8 (329)
Between–group difference [95% CI][a)]	-	-7.46 [-10.81, -4.11]	-3.67 [-7.02, -0.32]	-14.62 [-17.95, -11.29]
P value[a)]	-	$P < 0.001$	$P = 0.032$	$P < 0.001$

Mean ± SD (No. of patients)
a) A model of analysis of covariance (ANCOVA) with group, baseline value, medical institution, and interaction between group and medical institution as explanatory variables

AEs were observed in 22.0% (72 of 327) of patients in CLDM/BPO Gel, 1%/3%, group; in 25.3% (83 of 328) of patients in the 1% CLDM group; in 31.1% (102 of 328) of patients in the 3% BPO group; and in 26.2% (87 of 332) of patients in the gel base group. ADRs[164] were observed in 1.2% (4 of 327) of patients in CLDM/BPO Gel, 1%/3%, group; in 1.5% (5 of 328) of patients in the 1% CLDM group; in 2.4% (8 of 328) of patients in the 3% BPO group; and in 1.5% (5 of 332) of patients in the gel base group. Table 28 summarizes AEs and ADRs observed in ≥2% of patients in any group.

Table 28. Adverse events and adverse drug reactions reported by ≥2% of participants in any group (ITT population)

Adverse events	Adverse events				Adverse drug reactions			
	CLDM/BPO, 1%/3%	1% CLDM	3% BPO	Gel base	CLDM/BPO, 1%/3%	1% CLDM	3% BPO	Gel base
No. of patients	327	328	328	332	327	328	328	332
Overall	72 (22.0)	83 (25.3)	102 (31.1)	87 (26.2)	4 (1.2)	5 (1.5)	8 (2.4)	5 (1.5)
Nasopharyngitis	27 (8.3)	23 (7.0)	32 (9.8)	19 (5.7)	0	0	0	0
Upper respiratory tract infection	11 (3.4)	13 (4.0)	13 (4.0)	13 (3.9)	0	0	0	0
Headache	4 (1.2)	8 (2.4)	9 (2.7)	7 (2.1)	0	0	0	0

No. of patients (%)

No deaths occurred during the study. Depression, a serious AE,[165] developed in 1 patient in the 3% BPO group. A causal relationship to the study gel was ruled out. AEs leading to treatment discontinuation were observed in 5 patients, which included application site dermatitis in 1 patient in CLDM/BPO Gel, 1%/3%, group, application site pruritus and application site hypersensitivity in 1 patient each in the 3% BPO group, and application site pruritus and varicella in 1 patient each in the gel base group. A causal relationship to the study gel was ruled out for varicella, while it was not ruled out for all other events. The outcome was "not recovered/not resolved" at the discontinuation of the study for 1 event of application site pruritus, and "recovered/resolved" for the other events.

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Efficacy

PMDA reviewed as follows and concluded that the efficacy of CLDM/BPO Gel, 1%/3%, has been demonstrated. However, based on the situation of CLDM-resistant *P. acnes* in foreign countries [see "3.(i).B.(2) Resistance to CLDM"], there is a concern that *P. acnes* may become further resistant to CLDM in Japan. The applicant should continue to collect post-marketing information on resistance to CLDM and appropriately provide the information to healthcare professionals in clinical settings.

This conclusion will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(1).1) Results of efficacy evaluation

The applicant's explanation on the efficacy of CLDM/BPO Gel, 1%/3%:

[164] ADRs were defined as AEs for which a causal relationship to the treatment was rated as "possibly related," "probably related," or "definitely related" by the investigator.

[165] Outside the AE follow-up period, 1 patient in the 3% BPO group who had been lost to follow up was suspected to have gastric ulcer, which was classified as a serious AE. The patient was also reported to be possibly pregnant.

As Table 29 summarizes the change in the total number of lesions from baseline to Week 12 in the ITT population in Japanese phase III study (Study STF115287), a pairwise comparison between the CLDM/BPO, 1%/3%, twice-daily group and the 1% CLDM twice-daily group revealed a statistically significant difference, which demonstrates the superiority of twice-daily treatment with CLDM/BPO Gel, 1%/3%, over twice-daily treatment with 1% CLDM gel.

Table 29. Change in the total number of lesions from baseline to Week 12 of treatment (ITT population, from Table 21)

	CLDM/BPO, 1%/3%, once daily	CLDM/BPO, 1%/3%, twice daily	1% CLDM twice daily
Baseline	76.3 ± 30.05 (204)	80.2 ± 36.05 (296)	79.6 ± 37.76 (299)
Week 12 of treatment	20.7 ± 24.35 (201)	19.8 ± 20.73 (289)	30.6 ± 36.22 (299)
Change	-55.1 ± 29.59 (201)	-60.4 ± 34.58 (289)	-48.9 ± 34.92 (299)
Between-group difference with the 1% CLDM twice-daily [95% CI] [a)]	-8.2 [-12.9, -3.6]	-11.0 [-15.0, -7.0]	
P value[a)]	-	*P < 0.001*	

Mean ± SD (No. of patients)
a) A model of analysis of covariance (ANCOVA) with group, baseline value, and medical institution as explanatory variables

As Table 30 shows the changes in the numbers of inflammatory and non-inflammatory lesions from baseline to Week 12 in the ITT population, CLDM/BPO Gel, 1%/3%, is expected to be effective for the treatment of inflammatory and non-inflammatory lesions when it is applied to the affected skin once daily or twice daily [see "3.(i).B.(1) Mechanism of action of BPO and the effect of a combination of CLDM and BPO in the treatment of acne vulgaris"].

Table 30. Changes in the numbers of inflammatory and non-inflammatory lesions from baseline to Week 12 (ITT population)

		CLDM/BPO, 1%/3%, once daily	CLDM/BPO, 1%/3%, twice daily	1% CLDM twice daily
No. of inflammatory lesions	Baseline	28.7 ± 11.09 (204)	28.7 ± 11.05 (296)	28.7 ± 11.56 (299)
	Week 12 of treatment	5.9 ± 14.24 (201)	5.4 ± 8.03 (289)	8.4 ± 12.21 (299)
	Change	-22.6 ± 15.16 (201)	-23.2 ± 11.40 (289)	-20.3 ± 12.43 (299)
	Between-group difference with the 1% CLDM twice-daily [95% CI] [a)]	-2.6 [-5.0, -0.3]	-2.8 [-4.6, -1.0]	-
No. of non-inflammatory lesions	Baseline	47.7 ± 25.79 (204)	51.5 ± 30.31 (296)	50.9 ± 32.66 (299)
	Week 12 of treatment	14.8 ± 16.94 (201)	14.4 ± 15.89 (289)	22.2 ± 30.12 (299)
	Change	-32.5 ± 22.95 (201)	-37.2 ± 28.26 (289)	-28.7 ± 29.84 (299)
	Between-group difference with the 1% CLDM twice-daily [95% CI] [a)]	-5.6 [-9.5, -1.7]	-8.2 [-11.6, -4.8]	-

Mean ± SD (No. of patients)
a) A model of analysis of covariance (ANCOVA) with group, baseline value, and medical institution as explanatory variables

Thus the efficacy of CLDM/BPO Gel, 1%/3%, for the treatment of acne vulgaris has been demonstrated.

PMDA's view:

Since the superiority of twice-daily treatment with CLDM/BPO Gel, 1%/3%, over twice-daily treatment with 1% CLDM has been shown in Japanese phase III clinical study (Study STF115287), the efficacy of CLDM/BPO Gel, 1%/3%, has been demonstrated. Also, since the numbers of inflammatory and non-inflammatory lesions decreased in patients in whom CLDM/BPO Gel, 1%/3%, was applied once daily or twice daily in Japanese phase III clinical study (Study STF115287), CLDM/BPO Gel, 1%/3%, is expected to be effective in the treatment of both types of lesions.

4.(iii).B.(1).2) Efficacy of CLDM/BPO Gel, 1%/3%, by clinical isolates

The applicant explained the efficacy of CLDM/BPO Gel, 1%/3%, and 1% CLDM by clinical isolates obtained in the clinical studies in Japan as follows:

As shown in Table 31, the isolation and identification rates of *P. acnes* and *S. epidermidis* did not differ among the groups in the Japanese phase III study (Study STF115287), and *P. acnes* was isolated from approximately 75% of patients, while *S. epidermidis* was isolated from approximately 45% of patients. The isolation and identification rate of *S. aureus* was very low in all groups. According to the change in the total number of lesions from baseline to Week 12 in subgroups (ITT population) stratified by type of bacteria isolated at baseline (Table 32), CLDM/BPO Gel, 1%/3%, is expected to be effective for the treatment of acne associated with all the bacteria assessed when CLDM/BPO Gel, 1%/3%, is applied once daily or twice daily.

Table 31. Isolation and identification rates of clinical isolates at baseline (ITT population)

Clinical isolates	CLDM/BPO, 1%/3%, once daily	CLDM/BPO, 1%/3%, twice daily	1% CLDM twice daily
No. of patients	204	296	299
P. acnes	154 (75)	225 (76)	220 (74)
S. aureus	8 (4)	6 (2)	7 (2)
S. epidermidis	88 (43)	133 (45)	140 (47)

No. of patients (%)

Table 32. Change in the total number of lesions from baseline to Week 12 by clinical isolates at baseline (ITT population)

	CLDM/BPO, 1%/3%, once daily		CLDM/BPO, 1%/3%, twice daily		1% CLDM twice daily	
	No. of strains	Change [95% CI]	No. of strains	Change [95% CI]	No. of strains	Change [95% CI]
Clinical isolates at baseline						
P. acnes	153	-55.8 [-60.4, -51.1]	219	-61.9 [-66.5, -57.2]	220	-51.1 [-55.7, -46.5]
S. aureus	8	-58.9 [-82.7, -35.1]	6	-38.2 [-70.2, -6.2]	7	-32.9 [-80.3, 14.6]
S. epidermidis	87	-56.3 [-62.9, -49.8]	129	-62.0 [-68.3, -55.6]	140	-50.6 [-56.6, -44.5]

Mean

PMDA's view:

On the basis of changes in the total number of lesions from baseline to Week 12 by clinical isolates at baseline in the Japanese phase III clinical study (Study STF115287), CLDM/BPO Gel, 1%/3%, is considered effective against all types of bacteria assessed in the study.

4.(iii).B.(1).3) Efficacy by age

The applicant's explanation on the efficacy of CLDM/BPO Gel, 1%/3%, by age:

The Japanese phase III clinical study (Study STF115287) enrolled patients 12 to 45 years of age. As Table 33 shows, both in younger and older patient subgroups (ITT population), the change in the total number of lesions from baseline to Week 12 was higher in patients receiving CLDM/BPO Gel, 1%/3%, once daily or twice daily than those receiving 1% CLDM twice daily.

Table 33. Change in the total number of lesions from baseline to Week 12 by age (ITT population)

	CLDM/BPO, 1%/3%, once daily		CLDM/BPO, 1%/3% twice daily		1% CLDM twice daily	
	No. of patients	Change [95% CI]	No. of patients	Change [95% CI]	No. of patients	Change [95% CI]
12 to 15 years of age	48	-67.3 [-76.7, -57.8]	65	-63.7 [-72.5, -55.0]	59	-48.6 [-59.8, -37.4]
16 to 45 years of age	153	-51.3 [-55.8, -46.9]	224	-59.4 [-63.9, -54.9]	240	-49.0 [-53.2, -44.9]

Mean

PMDA's view:

In patients 12 to 15 years of age, and those 16 to 45 years of age, the change in the total number of lesions from baseline to Week 12 was larger in the CLDM/BPO, 1%/3%, once-daily and twice-daily treatment groups than in the 1% CLDM twice-daily treatment group. It is thus considered that the efficacy of CLDM/BPO Gel, 1%/3%, has been demonstrated in both age groups and does not differ substantially by age.

4.(iii).B.(2) Safety

PMDA reviewed the safety of CLDM/BPO Gel, 1%/3%, and 3% BPO as described in the following sections focusing mainly on the Japanese phase III clinical studies (Studies STF115287 and STF115288), and concluded that the safety of CLDM/BPO Gel, 1%/3%, is acceptable for the following reasons: CLDM/BPO Gel, 1%/3%, caused AEs such as dry skin, erythema, dermatitis contact, pruritus, skin exfoliation, dermatitis exfoliative, skin irritation, facial pain, and burning sensation at the application sites, but most of the AEs were mild or moderate in severity, and all resolved or improved during treatment, or after temporary or permanent discontinuation of treatment. However, the applicant should provide information on the following findings and possibilities to healthcare professionals in clinical settings appropriately, using information leaflets among other materials, and continue to collect relevant information after the market launch: the findings that the incidence of application site AEs were higher in patients receiving CLDM/BPO Gel, 1%/3%, than in those receiving gel base or 1% CLDM twice daily, and that the incidence of application site AEs tended to be higher in patients receiving CLDM/BPO Gel, 1%/3%, twice daily than in those receiving it once daily; the possibilities that safety of CLDM/BPO Gel, 1%/3%, may differ by gender, and that CLDM/BPO Gel, 1%/3%, may induce serious hypersensitivity reactions.

The above conclusion will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(2).1) Safety profile

Table 34 outlines safety findings in Japanese phase III clinical studies (Studies STF115287 and STF115288).

Table34. Outline of safety

	Study STF115287			Study STF115288	
	CLDM/BPO, 1%3%, once daily	CLDM/BPO, 1%/3%, twice daily	1% CLDM twice daily	3% BPO once daily	Gel base
No. of patients	204	296	299	178	182
Adverse events	108 (52.9)	163 (55.1)	110 (36.8)	103 (57.9)	86 (47.3)
Adverse drug reactions	49 (24.0)	104 (35.1)	27 (9.0)	54 (30.3)	10 (5.5)
Adverse events at the application site	60 (29.4)	114 (38.5)	41 (13.7)	58 (32.6)	14 (7.7)
Adverse drug reactions at the application site	49 (24.0)	103 (34.8)	27 (9.0)	52 (29.2)	7 (3.8)
Death	0	0	0	0	0
Serious adverse events	0	0	0	0	0
Adverse events leading to treatment discontinuation	17 (8.3)	27 (9.1)	7 (2.3)	12 (6.7)	5 (2.7)

No. of patients (%)

Safety by age was as follows. The incidence of AEs in the Japanese phase III study (Study STF115287) was, in patients ≤15 years of age, 41.7% (20 of 48) of patients in the CLDM/BPO, 1%/3%, once-daily group and 41.5% (27 of 65) of patients in the CLDM/BPO, 1%/3% twice-daily group, and 42.4% (25 of 59) of patients in the 1% CLDM twice-daily group; and, in patients ≥16 years of age, 56.4% (88 of 156) of patients, 58.9% (136 of 231) of patients, and 35.4% (85 of 240) of patients in the respective groups. The incidence of AEs in the other Japanese phase III study (Study STF115288) was, in patients ≤15 years of age, 62.2% (23 of 37) of patients in the 3% BPO group, and 41.7% (10 of 24) of patients in the gel base group; and, in patients ≥16 years of age, 56.7% (80 of 141) of patients, and 48.1% (76 of 158) of patients in the respective groups.

PMDA decided to evaluate the safety of CLDM/BPO Gel, 1%/3%, at the application site in the following section because Japanese phase III clinical studies (Studies STF115287 and STF115288) showed that the occurrence of AEs and ADRs at application site appear to be more common in patients using CLDM/BPO Gel, 1%/3%, than in those using 1% CLDM twice daily. There are no particular differences in adverse event profiles between the age groups.

4.(iii).B.(2).2) Safety at the application site

PMDA asked the applicant to explain whether there are particular tendencies in the occurrence of AEs at the application site.

The applicant's explanation:

As Table 35 shows, AEs that developed at the application site in ≥2% of patients in any patient group in Japanese phase III studies (Studies STF115287 and STF115288) were similar to those observed on the face after application of 3% BPO gel. CLDM/BPO Gel, 1%/3%, did not tend to increase the occurrence of AEs at the application site. The incidence of AEs associated with CLDM/BPO Gel, 1%/3%, tended to be lower in the once-daily treatment group than in the twice-daily treatment group.

Table 35. Adverse events at the application site reported by ≥2% of participants in any group

Adverse events	Study STF115287			Study STF115288	
	CLDM/BPO, 1%/3%, once-daily	CLDM/BPO, 1%/3%, twice-daily	1% CLDM twice-daily	3% BPO	Gel base
No. of patients	204	296	299	178	182
All events	60 (29.4)	114 (38.5)	41 (13.7)	58 (32.6)	14 (7.7)
Dry skin	17 (8.3)	35 (11.8)	8 (2.7)	13 (7.3)	4 (2.2)
Erythema	8 (3.9)	22 (7.4)	8 (2.7)	8 (4.5)	2 (1.1)
Dermatitis contact	12 (5.9)	23 (7.8)	4 (1.3)	15 (8.4)	0
Pruritus	9 (4.4)	17 (5.7)	6 (2.0)	11 (6.2)	3 (1.6)
Skin exfoliation	4 (2.0)	25 (8.4)	2 (0.7)	3 (1.7)	2 (1.1)
Dermatitis exfoliative	4 (2.0)	6 (2.0)	4 (1.3)	0	0
Skin irritation	3 (1.5)	8 (2.7)	2 (0.7)	6 (3.4)	1 (0.5)
Facial pain	9 (4.4)	9 (3.0)	4 (1.3)	18 (10.1)	2 (1.1)
Burning sensation	6 (2.9)	12 (4.1)	4 (1.3)	2 (1.1)	0

No. of patients (%)

Skin and subcutaneous tissue disorders[166] on the face associated with the application of CLDM/BPO Gel, 1%/3%, or 3% BPO gel tended to develop more commonly in the early phase of treatment (Table 36).

Table 36. Incidence of skin and subcutaneous tissue disorders by time on treatment

Skin and subcutaneous tissue disorders	Day of treatment				
	Days 1 to 7	Days 8 to 14	Days 15 to 28	Days 29 to 56	Day 57 or thereafter
Study STF115287					
CLDM/BPO, 1%/3%, once-daily Group	21/204 (10.3)	17/198 (8.6)	14/193 (7.3)	5/188 (2.7)	10/185 (5.4)
CLDM/BPO, 1%/3%, twice-daily Group	53/296 (17.9)	45/285 (15.8)	13/274 (4.7)	12/269 (4.5)	9/263 (3.4)
Study STF115288					
3% BPO group	21/178 (11.8)	14/177 (7.9)	19/177 (10.7)	14/173 (8.1)	6/164 (3.7)

No. of patients (%)

Of 63 patients with moderate AEs categorized as "skin and subcutaneous tissue disorders", 46 patients (15 of 18 in the CLDM 1%/BPO 3% once-daily group, 20 of 31 in the CLDM/BPO, 1%/3%, twice-daily group, and 11 of 14 in the 3% BPO group) discontinued the treatment temporally or permanently. However, most of the AEs of this category were mild or moderate in severity, and all AEs resolved or improved during treatment or after temporary or permanent discontinuation of treatment.[167]

PMDA's view:

The applicant should provide the following information on the application site AEs to healthcare professionals in clinical settings appropriately using information leaflets among other materials: most moderate AEs led to temporal or permanent discontinuation of treatment; AEs developed more often in patients receiving CLDM/BPO Gel, 1%/3%, than in those receiving 1% CLDM or gel base; and AEs

[166] Adverse events classified by Systemic Organ Class (SOC) in MedDRA to "skin and subcutaneous tissue disorders"
[167] Except for 1 patient in the CLDM/BPO, 1%/3% twice-daily group who experienced "acne" after discontinuation of the treatment.

tended to develop more often in patients using the proposed drug twice daily than in those using it once daily. Additionally, the applicant should collect post-marketing information on the safety of CLDM/BPO Gel, 1%/3%, including occurrence of application site AEs.

4.(iii).B.(2).3) Gender difference in safety

The applicant's explanation on the gender difference in safety of CLDM/BPO Gel, 1%/3%:

As Table 37 shows, the incidence of dry skin, facial pain, and dermatitis contact in Japanese phase III clinical studies (Studies STF115287 and STF115288) were higher in female patients than in male patients. This gender difference may be explained by the fact that females are prone to developing dry skin since females have a thinner stratum corneum and lower androgen levels than in males. Makeup is another factor that may lead to dry skin. Dry skin causes destruction of stratum corneum. Accelerated skin turnover to replace the damaged stratum corneum may lead to the development of incomplete layer with poor barrier function, and thereby lead to sensitive skin.

Table 37. Incidence rates of dry skin, facial pain, and contact dermatitis in males and females

	Adverse events	Study STF115287			Study STF115288	
		CLDM/BPO, 1%/3%, once daily	CLDM/BPO, 1%/3%, twice-daily	1% CLDM twice-daily	3% BPO	Gel base
Males	No. of patients	65	109	97	60	66
	Dry skin	3 (4.6)	7 (6.4)	2 (2.1)	4 (6.7)	4 (6.1)
	Facial pain	2 (3.1)	1 (0.9)	0	3 (5.0)	0
	Dermatitis contact	3 (4.6)	5 (4.6)	2 (2.1)	2 (3.3)	1 (1.5)
Females	No. of patients	139	187	202	118	116
	Dry skin	14 (10.1)	28 (15.0)	6 (3.0)	12 (10.2)	2 (1.7)
	Facial pain	7 (5.0)	8 (4.3)	4 (2.0)	16 (13.6)	2 (1.7)
	Dermatitis contact	11 (7.9)	19 (10.2)	3 (1.5)	14 (11.9)	1 (0.9)

No. of patients (%)

PMDA's view:

The applicant provided an acceptable explanation on why dry skin, facial pain, and contact dermatitis were more common in females than in males in Japanese phase III studies (Studies STF115287 and STF115288). However, the applicant should also provide relevant information regarding this gender difference to healthcare professionals in clinical settings using information leaflets among other materials, and encourage healthcare professionals to take appropriate measures, according to the condition, such as using moisturizers and suspending treatment for the treatment of any adverse events on the face, let alone dry skin, facial pain, and contact dermatitis.

4.(iii).B.(2).4) Safety information outside Japan

The applicant explained the safety profile of CLDM/BPO Gel, 1%/3%, in foreign countries as follows:

In June 2014, the U.S. Food and Drug Administration warned of serious hypersensitivity reactions with certain over-the-counter topical acne products containing BPO or salicylic acid.[168)] Accordingly, the Company Core Safety Information and the draft package insert for CLDM/BPO Gel, 1%/3%, describe

[168)] http://www.fda.gov/Drugs/DrugSafety/ucm400923.htm. Accessed October 2014.

precautions for hypersensitivity reactions to CLDM/BPO Gel, 1%/3%. No evidence or information on the cause of these hypersensitivity reactions has been obtained.

PMDA considers that information on the risk of hypersensitivity reactions should be provided appropriately to healthcare professionals in clinical settings in order to ensure appropriate measures are taken to handle such reactions.

4.(iii).B.(3) Clinical significance of combination formulation

PMDA asked the applicant to compare the efficacy of CLDM/BPO Gel, 1%/3%, with CLDM and BPO monotherapies, and explain the clinical significance of the proposed combination formulation.

The applicant's explanation:

The significance of combining CLDM and BPO was assessed in the Japanese phase III clinical study (Study STF115287) in terms of change in the number of total lesions from baseline to Week 12 of treatment and a superiority of CLDM/BPO, 1%/3%, twice-daily treatment over 1% CLDM twice-daily treatment [see "4.(iii).B.(1) Efficacy"]. In a foreign phase III study (Study W0261-301), the efficacy of once-daily application of CLDM/BPO, 1%/3%, was confirmed in a comparison with once-daily application of 1% CLDM in terms of the changes in the numbers of total, inflammatory, and non-inflammatory lesions from baseline to Week 12 of treatment as well as the Investigator's Global Assessment at Week 12 [see "4.(iii).A.(3) Foreign phase III study"].

It has been reported that tertiary amines such as CLDM promote the decomposition of BPO into benzoic acid and thereby increase the production of ROS.[169)] It is thus considered that CLDM enhances the bactericidal activity of BPO. No studies to compare efficacy or safety between CLDM/BPO Gel, 1%/3%, and BPO monotherapy were conducted in Japanese patients with acne vulgaris. However, the 2 Japanese phase III clinical studies (Studies STF115287 and STF115288) were conducted with similar inclusion criteria and efficacy endpoints.[170)] Table 38 outlines the findings at Week 12 of treatment in the 2 studies. Although care should be taken to compare the results of different studies, the efficacy of once-daily and twice-daily applications of CLDM/BPO Gel, 1%/3%, were superior to that of once-daily application of 3% BPO.

[169)] Burkhart CN, et al. *Skin Pharmacol Appl Skin Physiol.* 2000;13:292-296

[170)] Only in Study STF115287, a Japanese phase III clinical study, there was an efficacy measure of "susceptibility (MIC) of clinical isolates obtained before and after treatment against antimicrobial agents," and patients with a current or past history of localized enteritis, inflammatory bowel diseases (ulcerative colitis, pseudomembranous colitis, chronic diarrhoea, antibiotic-associated colitis, and diarrhoea haemorrhagic) or similar symptoms were excluded from the study.

Table 38. Efficacy at Week 12 of treatment in Japanese phase III studies (Studies STF115287 and STF115288) (ITT population)

Study	Study STF115287			Study STF115288	
Treatment group	CLDM/BPO, 1%/3%, once daily	CLDM/BPO, 1%/3%, twice daily	1% CLDM twice daily	3% BPO once daily	Vehicle once daily
No. of patients	204	296	299	178	182
Change from baseline[a)]					
Total number of lesions	-51	-51	-44	-40	-24
No. of inflammatory lesions	-21	-20	-19	-17	-11
No. of non-inflammatory lesions	-27	-29	-24	-20	-13
Percent change from baseline[a)]					
Total number of lesions	-80.56%	-81.25%	-71.19%	-69.23%	-40.65%
No. of inflammatory lesions	-88.64%	-88.24%	-82.35%	-71.70%	-46.15%
No. of non-inflammatory lesions	-76.19%	-77.12%	-68.49%	-68.18%	-41.82%
Patients with ≥50% reduction in the total number of lesions (%)	85%	89%	79%	66%	40%
Patients achieving ≥2-point improvement in ISGA score from baseline (%)	30%	31%	14%	19%	1%
Patients with ISGA score of 0 (clear) or 1 (almost clear)	30%	34%	20%	21%	2%

a) Median

Considering that a superiority of once-daily treatment with CLDM/BPO Gel, 1%/3%, over 3% BPO once-daily treatment was demonstrated in terms of changes in the numbers of total and inflammatory lesions from baseline to Week 12, and the Investigator's Global Assessment at Week 12 in Study W0261-301, a foreign phase III study, CLDM/BPO Gel, 1%/3%, is expected to be more effective than 3% BPO gel [see "4.(iii).A.(3) Foreign phase III study"].

The applicant considered that the results of these clinical studies in and outside Japan indicate the clinical significance of the combination formulation.

PMDA's view:

Since the superiority of CLDM/BPO Gel, 1%/3%, over 1% CLDM gel was demonstrated in the Japanese phase III study (Study STF115287), the clinical significance of BPO combination in CLDM/BPO Gel, 1%/3%, was confirmed in a comparison with CLDM monotherapy. Although no clinical studies have been conducted in Japan to demonstrate the clinical significance of CLDM combination in CLDM/BPO Gel, 1%/3%, as compared with BPO monotherapy, the foreign phase III study (Study W0261-301) has demonstrated the superiority of once-daily application of CLDM/BPO Gel, 1%/3%, over once-daily application of 3% BPO. The results of the Japanese phase III studies (Studies STF115287 and STF115288) are consistent with those of the foreign phase III study (Study W0261-301) although care should be taken to interpret the results of comparing different studies. Consequently, the clinical significance of CLDM/BPO combination in CLDM/BPO Gel, 1%/3%, over BPO monotherapy may be expected.

The above conclusion will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(4) CLDM resistance of *P. acnes*

The applicant explained the CLDM/BPO combination effects on preventing the development of CLDM-resistant strains of *P. acnes* as follows:

CLDM-resistant *P. acnes* has become a problem as the resistance rate of *P. acnes* to CLDM[171] was reported to be 79% in the US (1983), 91% in Spain (2003), 55.5% in the UK (2003), and 53.5% in Hong Kong (2013).[172] It has been reported that multiple applications of CLDM monotherapy induced the development of CLDM-resistant *P. acnes*, a primary causative bacteria for the target illness, after 8 weeks of topical treatment or thereafter, while multiple applications of a CLDM/BPO combination gel did not show such tendency.[173] Because these findings suggest that part of the significance of CLDM/BPO combination is to prevent the development of CLDM-resistant *P. acnes* as compared with CLDM monotherapy, the effect of CLDM/BPO Gel, 1%/3%, in inhibiting the development of CLDM-resistant *P. acnes* was investigated in the Japanese phase III study (Study STF115287).

Table 39 summarizes the resistance rate of *P. acnes* to CLDM[174] in patients in whom CLDM/BPO Gel, 1%/3%, once daily or twice daily or 1% CLDM twice daily was applied, and the MICs of CLDM against clinical isolates were determined at baseline and Week 12. The resistance rate did not differ between patients in whom CLDM/BPO Gel, 1%/3%, was applied and those in whom CLDM monotherapy was. The data did not demonstrate that CLDM/BPO Gel, 1%/3%, inhibits the development of CLDM resistance more than CLDM monotherapy does.

Table 39. MICs of CLDM against *P. acnes* isolated before and after treatment

Clinical isolates	Treatment	Timing of sampling	No. of isolates	MIC (μg/mL)		
				Range	MIC_{90}	Resistance rate (No. of isolates)[a]
P. acnes	CLDM/BPO, 1%/3%, once daily	Baseline	12	0.12 - 128	1	8.3% (1)
		Week 12 of treatment	12	≤0.06 - >128	>128	16.7% (2)
	CLDM/BPO, 1%/3%, twice daily	Baseline	17	0.12 - >128	128	29.4% (5)
		Week 12 of treatment	17	0.12 - >128	128	35.3% (6)
	1% CLDM twice daily	Baseline	51	≤0.06 - >128	128	23.5% (12)
		Week 12 of treatment	51	0.12 - >128	>128	27.5% (14)

a) Resistance breakpoint, *P. acnes* ≥8 μg/mL (Ishida N, et al. *Microbiol Immunol*, 52: 621-624, 2008)

Currently, the resistance rate of *P. acnes* to CLDM is lower in Japan than in other countries, and CLDM is considered effective in the treatment of acne vulgaris in Japan. However, in light of the following facts, the possibility cannot be ruled out that resistance rate of *P. acnes* to CLDM will increase in Japan in the future: (1) the major cause of acne vulgaris is *P. acnes*, a common human skin bacterium[175]; (2)

[171] The resistance rate was reported as the percentage of resistant isolates in all isolates tested, or as the percentage of patients who had at least one strain of resistant *P. acnes* in patients from whom *P. acnes* was isolated.
[172] Dreno B, et al. *Eur J Dermatol.* 2014;doi:10.1684/ejd.2014.2309
[173] Cunliffe WJ, et al. *Clin Ther.* 2002;24:1117-1133
[174] A clinical isolate with a MIC of ≥8 μg/mL was defined as CLDM resistant. The resistance rate was calculated as the percentage of resistant isolates in all isolates.
[175] Nakase K, et al. *Jpn J Dermatol.* 2012;794-796

the mechanism of the development of drug-resistant *P. acnes*[176] is considered not to differ in and outside Japan; (3) the resistance rate of *P. acnes* to CLDM increased during approximately 10 years from the 1980s to 1990s in foreign countries[177, 178]; (4) cross resistance has been demonstrated between macrolides and lincomycin derivatives including CLDM[179]; (5) long-term administration of macrolides for the treatment of severe acne vulgaris[180] may cause the development of CLDM resistance. Since a foreign study report has suggested that CLDM/BPO combination gels prevent the development of CLDM-resistant *P. acnes*, CLDM/BPO Gel, 1%/3%, is expected to prevent the development of CLDM-resistant *P. acnes* strains.

PMDA's view:

The resistance rate of *P. acnes* to CLDM has remained low in Japan and this is possibly the reason why CLDM/BPO Gel, 1%/3%, did not demonstrate inhibition of the development of CLDM-resistant *P. acnes* strains in the Japanese phase III study (Study STF115287). Since a foreign report has indicated that the combination of BPO and CLDM prevent the development of CLDM-resistant strains,[173] the applicant should continue to collect post-marketing information on CLDM-resistant *P. acnes* strains, and appropriately provide the information to healthcare professionals in clinical settings when new findings become available.

4.(iii).B.(5) Clinical positioning

The applicant explained the clinical significance of CLDM/BPO Gel, 1%/3%, for the treatment of acne vulgaris as follows:

The Guidelines for the Treatment of Acne Vulgaris available in Japan[181] recommend the use of topical adapalene with a grade of recommendation of A[182] and topical antimicrobial agents with C2[183] for the treatment of comedones (non-inflammatory lesions), and no oral antimicrobial agents are recommended for this condition. The Guidelines recommend, with a grade of recommendation of A, topical antimicrobial agents for the treatment of papules and pustules (inflammatory lesions) regardless of severity,[184] topical adapalene for these conditions except very severe cases, and oral antimicrobial agents for these conditions except mild cases.

In the Japanese phase III study (Study STF115287), the clinical efficacy of CLDM/BPO Gel, 1%/3%, was confirmed in terms of the change in total number of lesions from baseline to Week 12. Topical

[176] Major mechanisms of resistance to macrolides include (1) point mutations at 3 different sites in the target site of macrolides (i.e., ribosome 23 rRNA mutations at positions 2057, 2058, and 2059) and (2) modifications of the target site through transcription of the erythromycin resistance methylase gene, erm(X). Both mechanisms of macrolide resistance have been confirmed in and outside Japan (Nakase K, et al. *Jpn J Dermatol.* 2012;794-796, Ross JI, et al. *Br J Dermatol.* 2001;144:339-346, Ishida N, et al. *Microbiol Immunol.* 2008;52:621-624).

[177] Cooper AJ, *Med J Aust.* 1998;169(5):259-261

[178] Dreno B, et al. *Eur J Dermatol.* 2014;24:330-334

[179] Point mutations in the base sequence at 3 different sites in the target site of macrolides (i.e., ribosome 23 rRNA mutations at positions 2057, 2058, and 2059) confer cross-resistance to lincomycin derivatives, including CLDM.

[180] Ishida N, et al. *Microbiol Immunol.* 2008;52:621-624

[181] Hayashi N, et al. *The Japanese Journal of Dermatology.* 2008;118:1893-1923

[182] Strongly recommended (with at least one level I [systematic review/metaanalysis] or good quality level II [more than one randomized comparative study] evidence for efficacy)

[183] Not recommended as there is no sufficient evidence to support use (absence of evidence for efficacy, or presence of evidence for inefficacy)

[184] Severity evaluation criteria based on the number of lesions: Mild, ≤5 inflammatory lesions on either side of face; moderate, 6 to 20 inflammatory lesions on either side of face; severe, 21 to 50 inflammatory lesions on either side of face; and very severe, ≥51 inflammatory lesions on either side of face.

CLDM products are indicated for the treatment of acne (with suppurative inflammation) and are available only for the treatment of inflammatory lesions. On the other hand, CLDM/BPO Gel, 1%/3%, was effective in the treatment of inflammatory and non-inflammatory lesions. CLDM/BPO Gel, 1%/3%, was not compared with topical adapalene in clinical studies in or outside Japan, and the difference in positioning of the 2 products in the treatment of comedones is unclear. However, the number of non-inflammatory lesions decreased from baseline to Week 12 in the Japanese phase III study (Study STF115287), which suggest that CLDM/BPO Gel, 1%/3%, is as effective in the treatment of non-inflammatory lesions as adapalene is.

Accordingly, CLDM/BPO Gel, 1%/3%, may be recommended for the treatment of acute acne vulgaris where both comedones (non-inflammatory lesions) and papules and pustules (inflammatory lesions) are present because it is also expected to prevent the progression from non-inflammatory to inflammatory lesions.

Most AEs observed in the Japanese phase III study (Study STF115287) were skin-related AEs, mild or moderate in severity. Because findings indicate that AEs tended to occur more frequently in an early phase of treatment, safety of treatment should be considered acceptable if the risk of these AEs is understood before treatment, and a decision on whether the treatment should be continued or not will be made on the basis of the benefits and risks of treatment if these AEs develop.

PMDA's view:
The results of the Japanese phase III study (Study STF115287) indicate the efficacy of CLDM/BPO Gel, 1%/3%, in the treatment of inflammatory and non-inflammatory lesions. CLDM/BPO Gel, 1%/3%, is thus expected to be effective in the treatment of acne vulgaris. Although the risk of application site AEs should be closely monitored, the safety of CLDM/BPO Gel, 1%/3%, is considered acceptable, since AEs observed were mild or moderate in severity and recovered or improved during treatment or after temporary or permanent discontinuation of treatment. On the basis of the above considerations, CLDM/BPO Gel, 1%/3%, may become a treatment option for acne vulgaris.

4.(iii).B.(6) Indication

On the basis of the reviews in Sections "4.(iii).B.(1) Efficacy" and "4.(iii).B.(2) Safety," PMDA concluded that the applicable microorganisms and indications for CLDM/BPO Gel, 1%/3%, may be set, respectively, as proposed, i.e., "*Staphylococcus* spp. and *Propionibacterium acnes* susceptible to Clindamycin Phosphate Hydrate/Benzoyl Peroxide" and "acne vulgaris." Post-marketing information should be collected for the safety of the treatment in patients <12 years and ≥46 years of age, who were not included in the clinical studies in or outside Japan. Precautions should be made to use the other appropriate treatment options for patients with severe lesions such as those with nodules and cysts who were excluded from the clinical studies of CLDM/BPO Gel, 1%/3%, in and outside Japan.

The above conclusion will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(7) Dosage and administration

On the basis of the reviews in Sections "4.(iii).B.(1) Efficacy" and "4.(iii).B.(2) Safety" and the following considerations, PMDA concluded that the dosage and administration for CLDM/BPO Gel, 1%/3%, may be set as proposed, i.e., " an appropriate amount of the gel should be applied once daily to the affected areas on the face after washing." In order to prevent the development of CLDM resistance among bacteria causing acne vulgaris, the precautions section in the package insert should include the following description: (1) in clinical studies in Japan, CLDM/BPO Gel, 1%/3%, was applied for up to 12 weeks, and detailed data on longer-term treatment are not available; and (2) the treatment with CLDM/BPO Gel, 1%/3%, should be limited to the minimum period necessary. As CLDM/BPO Gel, 1%/3%, was applied only to the face in clinical studies to investigate the effect of facial skin lesions, this information should be communicated.

The above conclusion will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(7).1) Rationales for the concentration of BPO and application frequency

The applicant explained that the concentration of CLDM was set at 1%, the same concentration as in topical CLDM products approved in Japan. The applicant rationalized the concentration of BPO at 3% and the application frequency of once daily as follows:

A topical gel containing 1% CLDM and 5% BPO was approved in foreign countries in 1999. It has been reported that BPO causes skin irritation symptoms accompanied by erythema, skin exfoliation, and pruritus by stimulating the skin in a concentration-dependent manner,[185),186)] and that the efficacy of BPO appears to remain mostly unchanged over its concentration range of 2.5 to 10%.[187)] On the basis of these findings, CLDM/BPO gels containing a lower concentration of BPO was developed to achieve efficacy similar to that obtained with the CLDM/BPO gel, 1%/5%, with a lower risk of skin irritations by BPO.

In Study 159, the foreign phase II study, the changes in the numbers of inflammatory and non-inflammatory lesions from baseline to the end of treatment did not clearly show a concentration-dependent response among CLDM/BPO gels, 1%/5%, 1%/4%, and 1%/2%, and all of these combination ratios were effective. The Investigator's Global Assessment (IGA) scores tended to be lower in the CLDM/BPO, 1%/2%, group than in the other 2 groups. The incidence of AEs at the application site tended to be lower in the CLDM/BPO, 1%/2%, group than in the other 2 groups. These findings suggest that BPO is not sufficiently effective at 2%, and may pose a risk to safety at 4% or higher concentration.

Methylparaben (MP),[188)] a preservative contained in the CLDM/BPO, 1%/5%, product approved outside Japan, is known to lead to allergic contact dermatitis. Because BPO has an antimicrobial activity and was considered to act as a preservative in CLDM/BPO Gel, 1%/3%, an antimicrobial preservative effectiveness was tested to determine an appropriate BPO concentration in the absence of MP. In the

185) Mills OH, et al. *Int J Dermatol.* 1986;25:664-667
186) Sagransky M, et al. *Expert Opin Pharmacother.* 2009;10:2555-2562
187) FDA, *Federal Register*, USA, 75 FR 9767. 2010
188) Zug KA, et al. *Dermatitis.* 2009;20:149-160

test, a formulation containing 2% BPO did not meet the requirements, while that containing 3% BPO satisfied the requirements.

On the basis of the results of the foreign phase II study and the antimicrobial preservative effectiveness test, the concentration of BPO in the topical antimicrobial product was set at 3% during the development of CLDM/BPO Gel, 1%/3%, outside Japan.

Since CLDM and BPO, the active ingredients of CLDM/BPO Gel, 1%/3%, were detected at trace levels in the blood, the systemic exposures to these substances were low, and thus, the 2 substances were considered not sensitive to ethnic factors from systemic point of view. Accordingly, during the development of the product in Japan, a formulation containing 3% BPO was employed in Study STF115287, a phase III study to investigate the efficacy and safety of CLDM/BPO Gel, 1%/3%, in Japanese patients.

Because the efficacy of the treatment at Week 12 did not differ between the once-daily and twice-daily treatment groups in the Japanese phase III study (Study STF115287) (Table 40), and the profiles of application site AEs suggests once-daily treatment is safer than twice-daily treatment, once-daily application was considered appropriate. As of August 2014, CLDM/BPO Gel, 1%/3%, is approved in 16 countries including the UK and Germany with an application frequency of once daily.

Table 40. Efficacy results at 12 weeks in Japanese phase III study (Study STF115287) (ITT population)

	CLDM/BPO, 1%/3%, once daily	CLDM/BPO, 1%/3%, twice daily	1% CLDM twice daily
No. of patients	204	296	299
Change from baseline[a)]			
Total number of lesions	-51	-51	-44
No. of inflammatory eruptions	-21	-20	-19
No. of non-inflammatory lesions	-27	-29	-24
Percent change from baseline[a)]			
Total number of lesions	-80.56%	-81.25%	-71.19%
No. of inflammatory lesions	-88.64%	-88.24%	-82.35%
No. of non-inflammatory lesions	-76.19%	-77.12%	-68.49%
Patients achieving ≥50% reduction in the total number of lesions from baseline	85%	89%	79%
Patients achieving ≥2-point improvement in ISGA score from baseline (%)	30%	31%	14%
Patients with ISGA score of 0 (clear) or 1 (almost clear)	30%	34%	20%

a) Median

PMDA's view:

The applicant's discussion is understandable in that since CLDM/BPO Gel, 1%/3%, is a topical gel, and the active ingredients CLDM and BPO are detected at trace levels in the blood, the systemic exposure to CLDM/BPO Gel, 1%/3%, is low, and thus ethnic factors are unlikely to influence the active ingredients from systemic point of view. However, it cannot be concluded that the safety of CLDM/BPO Gel, 1%/3%, at the application site (application site reactions) and antimicrobial susceptibility of causative organisms do not differ between Japanese and non-Japanese patients. Consequently, the

concentration of BPO should have been explored in clinical studies in Japan. Nonetheless, considering that the formulation containing 3% BPO showed antimicrobial activity in an antimicrobial preservative effectiveness test, and that the 3% BPO gel was confirmed effective with no particular safety concerns in the other Japanese phase III study (Study STF115288), BPO concentration of 3% is acceptable. In the Japanese phase III study (Study STF115287), the superiority of twice-daily application of CLDM/BPO Gel, 1%/3%, over 1% CLDM twice-daily application was demonstrated, and the efficacy of CLDM/BPO Gel, 1%/3%, did not differ between once-daily and twice-daily application. These findings indicate that once-daily application of CLDM/BPO Gel, 1%/3%, is expected to be effective and is likely to have a higher tolerability than twice-daily application, and therefore once-daily application is acceptable for this product.

4.(iii).B.(7).2) Maximum dosage

PMDA asked the applicant to explain whether the maximum daily dosage of CLDM/BPO Gel, 1%/3%, should be set or not.

The applicant's explanation:

Because the mean daily dose (mean ± SD) of CLDM/BPO Gel, 1%/3%, in the once-daily treatment group was 0.74 ± 0.25 g in the Japanese phase III study (Study STF115287), the daily dose was assumed to be 1 g. When CLDM/BPO Gel, 1%/3%, is applied to human skin surface, BPO is absorbed in the skin and metabolized into benzoic acid. When 1 g of CLDM/BPO Gel, 1%/3% (containing 30 mg of BPO) is applied to the skin, less than 1.5 mg of benzoic acid circulates in the blood because benzoic acid distributed in the systemic circulation is less than 5% of the dose applied to the skin.[189)] In a 60 kg human, the maximum systemic exposure to benzoic acid is calculated to be 0.025 mg/kg. The acceptable daily intake of benzoic acid is ≤5 mg/kg.[190)] The maximum systemic exposure to benzoic acid when CLDM/BPO Gel, 1%/3%, is used in routine clinical use is ≤1/200 of the acceptable daily intake.

In Study W0261-101, a foreign phase I study, where patients with acne vulgaris applied 4 g of CLDM/BPO Gel, 1%/3%, on the skin once daily for 5 days, the peak plasma concentration of CLDM (C_{max}) was 1.3 ± 1.0 ng/mL (mean ± SD). It has been reported that in healthy adults receiving a single intramuscular administration of CLDM at a dose of 300 mg, the mean serum CLDM concentration peaked at 3.11 μg/mL.[191)] The C_{max} obtained after a topical application of 4 g of CLDM/BPO Gel, 1%/3%, is approximately 1/2500 of the C_{max} after an intramuscular administration of CLDM at 300 mg.

Since systemic exposures to BPO and CLDM are extremely low when CLDM/BPO Gel, 1%/3%, is applied to the skin, it is not necessary to set the maximum daily dosage.

189) Nacht S, *J Am Acad Dermatol.* 1981;4:31-37
190) Tanimura A, Specifications and standards for food additives, eighth ed. 2007
191) Saito R, et al. *Jap J Antibiot.* 1977;30(3):228-233

PMDA considers the applicant's explanation that the maximum daily dosage may not be set for CLDM/BPO Gel, 1%/3%, is acceptable, but that a precaution not to use CLDM/BPO Gel, 1%/3%, at an excessively large amount is necessary.

4.(iii).B.(8) Post-marketing investigations

The applicant plans to conduct the drug use-results survey for CLDM/BPO Gel, 1%/3%, as follows after the market launch.

Drug use-results survey

- Purpose: To collect and assess data on the safety and efficacy of CLDM/BPO Gel, 1%/3%, in routine clinical use
- Target sample size: 2000 patients (1100 for safety analysis)
  Rationale for the sample size: In the Japanese phase III study (Study STF115287), contact dermatitis, an ADR, developed in 6.8% (34 of 500 patients). In order to collect data from a sufficient number of events to keep the confidence interval within 5% for the incidence of ADRs that develop in ≤10% of patients, the target sample size was set at 2000 (as the number of registered patients).
- Follow-up period: 12 weeks
- Survey period: 2 years and 3 months

PMDA considers that the following information should also be collected in the post-marketing surveillance of CLDM/BPO Gel, 1%/3%.

- Safety and efficacy in patients <12 years and ≥46 years of age
- Occurrence of adverse events at the application site
- Safety of CLDM/BPO Gel, 1%/3%, combined with conventional drugs for the treatment of acne vulgaris

Since the resistance rate of *P. acnes* to CLDM increased during a decade from the 1980s to 1990s in some foreign countries, and it is likely that resistance rate of *P. acnes* to CLDM will increase in Japan in the future, the applicant should continue to collect post-marketing information on resistance to CLDM, and appropriately provide the information to healthcare professionals in clinical settings when new findings become available.

This conclusion will be finalized, taking account of comments from the Expert Discussion.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

Document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

A GCP on-site inspection was conducted in accordance with the provisions of the pharmaceutical affairs act for the data submitted in the new drug application (5.3.5.1 STF115287 and 5.3.5.1 STF115288). As a result, PMDA concluded that the clinical studies as a whole were performed in compliance with GCP and there should be no problem with conducting a regulatory review based on the submitted application documents. The following findings observed in some of the medical institutions conducting clinical studies were communicated to the head of the relevant medical institution as points for improvement, although they will not affect the assessment of the clinical studies as a whole.

Points for improvement

Medical institutions

- Some participants meeting the exclusion criteria (using retinol, salicylic acid, or moisturizers containing alpha or beta-hydroxy acid on the face within 2 weeks before the study) were enrolled in the study, and the study gel was applied to them.

IV. Overall Evaluation

Based on the submitted data, the safety of CLDM/BPO Gel, 1%/3%, is acceptable in view of its expected benefits on the treatment of acne vulgaris. The product is expected to be beneficial in clinical settings. PMDA will discuss the following points at the Expert Discussion.

- Efficacy
- Safety
- Significance of the combination formulation of the product
- Indications
- Dosage and administration
- Post-marketing investigations

This application may be approved if the product is not considered to have any particular problems based on the comments from the Expert Discussion.

Review Report (2)

January 7, 2015

I. Product Submitted for Registration

[Brand name]	Duac Combination Gel
[Non-proprietary name]	Clindamycin Phosphate Hydrate/Benzoyl Peroxide
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	March 24, 2014

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations or other relevant information concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA administrative Rule No. 8/2008 dated December 25, 2008).

The expert advisors supported PMDA's conclusions described in the Review Report (1). PMDA conducted an additional review of the following points and took necessary actions.

(1) Risk management plan (draft)

Regarding PMDA's conclusion of the post-marketing surveillance of the product [see "4.(iii).B.(8) Post-marketing investigations"], the expert advisors provided the following comments.

- Clinical study data on the efficacy and safety of the product used concomitantly with other chemical substances in cosmetics or other products are limited. Such data should be collected continuously during post-marketing surveillance.

PMDA considers that the following information should be provided to healthcare professionals in clinical settings without delay when data are obtained during post-marketing surveillance.

- Safety and efficacy of the product in patients <12 years and ≥46 years of age
- Occurrence of adverse events at the application site
- Safety of the product when used with conventional drugs for the treatment of acne vulgaris
- Safety of the product when used with cosmetics or other chemicals

The resistance rate of *P. acnes* to CLDM increased during a decade from the 1980s to 1990s in foreign countries[50), 61)] [see "3.(i).B.(2) Resistance to CLDM"], and it is likely that resistance rate of *P. acnes* to CLDM will increase in Japan in the future. Therefore, the applicant should continue to collect post-

marketing information on resistance to CLDM, and appropriately provide the information to healthcare professionals in clinical settings when new findings become available.

PMDA requested the applicant to consider the above points, and the applicant accepted it.

In view of the above discussions on the draft risk management plan, PMDA concluded that it is appropriate to include the following safety and efficacy specifications (Table 41), and conduct additional pharmacovigilance activities and additional risk minimization actions (Table 42). A draft plan of the drug use-results survey was submitted (Table 43).

Table 41. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
・ Colitis (including antibiotic-associated colitis) ・ Skin irritation symptoms	・ Systemic hypersensitivity reactions	None
Efficacy specifications		
・ Efficacy in the clinical setting		

Table 42. Outline of additional pharmacovigilance activities and risk minimization actions in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization actions
・ Early post-marketing phase vigilance ・ Drug use-results survey	・ Early post-marketing phase vigilance

Table 43. Outline of the drug use-results survey (draft)

Purpose	Safety and efficacy evaluation in routine clinical use
Survey method	Central registration system
Participants	Patients with acne vulgaris
Survey period (Follow-up period)	2 years and 3 months (12 weeks)
Planned number of patients	2000 patients
Main survey items	Occurrence of colitis (including antibiotic-associated colitis); occurrence of skin irritation symptoms and systemic hypersensitivity reactions; occurrence of adverse events at the application site; safety of the product when used with conventional drugs for the treatment of acne vulgaris; safety of the product when used with cosmetics or other chemicals.

III. Overall Evaluation

As a result of its review, PMDA concludes that the product may be approved for the indication and the dosage and administration as shown below, with the following conditions. Since benzoyl peroxide is a new active ingredient, and the product is a new combination drug, the reexamination period should be the remaining of the reexamination period (until December 25, 2022) for Bepio Gel 2.5%, which contains benzoyl peroxide, an active ingredient of the product, which is not classified as a poisonous drug, a powerful drug, a biological product, or a specified biological product.

[Indications]	Applicable microorganisms *Staphylococcus* spp. and *Propionibacterium acnes* susceptible to Clindamycin Phosphate Hydrate/Benzoyl Peroxide Indication Acne vulgaris
[Dosage and administration]	An appropriate amount of Clindamycin Phosphate Hydrate/Benzoyl Peroxide Gel, 1%/3%, should be applied once daily to the affected areas on the face after washing.
[Conditions for approval]	The applicant is required to develop and appropriately implement a risk management plan.