Supplementary Material

Difamilast ointment in Japanese adult and pediatric patients with atopic dermatitis: A phase III, long-term, open-label study

Authors:

Hidehisa Saeki

Department of Dermatology, Nippon Medical School, Tokyo, Japan

Tomomi Imamura

Headquarters of Clinical Development, Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan

Daisuke Yokota

Headquarters of Clinical Development, Otsuka Pharmaceutical Co., Ltd., Osaka, Japan

Hidetsugu Tsubouchi

Medical Affairs, Otsuka Pharmaceutical Co., Ltd., Osaka, Japan

Corresponding Author:

Hidetsugu Tsubouchi

Medical Affairs,

Pharmaceutical Business Division,

Otsuka Pharmaceutical Co., Ltd.,

3-2-27 Otedori, Chuo-ku, Osaka 540-0021, Japan.

E-mail: Tsubouchi.Hidetsugu@otsuka.jp

Table S1 Investigator's Global Assessment score

Symptom	Severity score
No inflammatory signs of atopic dermatitis	0 = Clear
Just perceptible erythema and just perceptible papulation/infiltration	1 = Almost clear
Mild erythema and mild papulation / infiltration	2 = Mild disease
Moderate erythema and moderate papulation / infiltration	3 = Moderate disease
Severe erythema, and severe papulation / infiltration Severe erythema, and severe crusting papulation / infiltration with oozing	4 = Severe disease/very severe disease

Table S2 Full exclusion criteria

- Female children aged 7 to 14 years who are pregnant or possibly pregnant, or whose legal guardians are unable to agree to avoid sexual activity during the trial period and up until 30 days after the final administration of IMP
- Subjects who are pregnant, possibly pregnant, or breastfeeding, male subjects who desire to have their partner become pregnant, or female subjects of childbearing potential who desire to become pregnant, and who do not agree to either remain abstinent or employ at least two of the specified birth control methods (vasectomy, tubal ligation, vaginal diaphragm, IUD, birth control pill, condom with spermicide, etc) during the trial period and up until 30 days after the final administration of IMP
- Subjects who have rapid exacerbation of AD or contact dermatitis, within 28 days prior to the baseline examination
- Subjects who have a concurrent or history of skin disease other than AD (acne, psoriasis, etc) and who are judged inappropriate for assessment of AD in the present trial
- Subjects who have an active viral skin infection (eg, herpes simplex, herpes zoster, chicken pox) or clinical signs of such infection
- Subjects with a current or history of malignancy within the previous 5 years
- Subjects with a history of recurrent bacterial infection resulting in hospitalization or requiring intravenous antibiotic treatment within the past 2 years
- Subjects with a clinically significant complication or history of any of the following disorders that the investigator or subinvestigator judges would prevent safe conduct of the trial or impact efficacy assessment of the IMP:
    - Cardiac disease (eg, rheumatic fever or heart valve replacement)
    - Endocrinologic disease (eg, severe or uncontrolled diabetes)
    - Pulmonary disease
    - Neurologic disease
    - Psychiatric disease
    - Hepatic disease (eg, hepatitis B, hepatitis C carrier)
    - Renal disease
    - Hematologic disease
    - Immunologic or immunocompromised disease (eg, acquired immunodeficiency syndrome, Wiskott-Aldrich syndrome, carriers of HIV antibodies)
    - Other major disease (eg, systemic fungal infection) or other severe uncontrolled condition (eg, drug or alcohol abuse) judged by the investigator or subinvestigator to pose a health risk to the subject or to have the potential to impact efficacy assessment of the IMP
- Subjects who are judged by the investigator or subinvestigator to be unable to safely complete the trial based on laboratory results at screening examination
- Subjects who are judged by the investigator or subinvestigator to have a clinically abnormal blood pressure and pulse rate at the screening and baseline examinations

- Subjects who are judged by the investigator or subinvestigator to be unable to undergo blood sampling
- Subjects who are unable to stop treatment with UVA, NB-UVB, UVB, or biologics from 28 days prior to the baseline examination until the baseline examination
- Pediatric subjects who are unable to stop treatment with UVA, NB-UVB, or UVB from the baseline examination until the Week 52 examination
- Subjects who are unable to stop using systemic corticosteroids, systemic immunosuppressants, or systemic antimetabolites from 28 days prior to the baseline examination until the Week 52 examination
- Subjects who are unable to stop using topical corticosteroids for skin (excluding scalp) categorized as very strong or higher potency in the “Guidelines for Management of Atopic Dermatitis” from 21 days prior to the baseline examination until the Week 52 examination
- Subjects who are unable to stop using topical corticosteroids for skin (excluding scalp) categorized as strong potency in the “Guidelines for Management of Atopic Dermatitis” or topical corticosteroids other than those for skin or topical immunosuppressants (excluding scalp) from 7 days prior to the baseline examination until the Week 52 examination. However, intraocular, intra-nasal, intra-auricular, and inhaled corticosteroids and immunosuppressants may be considered if the investigator or subinvestigator judges that their use will not impact assessment of the affected area
- Subjects who are unable to stop using topical corticosteroids for skin (excluding scalp) categorized as low or medium potency in the “Guidelines for Management of Atopic Dermatitis” from 4 days prior to the baseline examination until the Week 52 examination
- Subjects with known hypersensitivity (including history) to any drugs (prescription, OTC, etc) or any ingredient of OPA-15406 ointment (eg, white petrolatum, mineral oil, paraffin, white wax, or propylene carbonate)
- Subjects with known plans to receive any of the prohibited concomitant drugs or therapies during the trial period
- Subjects who have participated in previous trials for OPA-15406 and have been administered the IMP
- Subjects who have used any other investigational drug within 4 months prior to the baseline examination or who are scheduled to participate in any other clinical trial during the trial period
- Subjects who have never been treated with a prescription medication for AD or who are satisfied with their current AD treatment regimen
- Subjects who do not respond at all to treatment with existing topical drugs for AD
- Subjects who are judged by the investigator or subinvestigator to be inappropriate to participate in the trial for any other reason

AD, atopic dermatitis; HIV, human immunodeficiency virus; IMP, investigational medicinal product; IUD, intrauterine device; NB-UVB, narrowband UVB; OPA-15406, difamilast; OTC, over-the-counter medicine; UVA, ultraviolet A; UVB, ultraviolet B

Table S3 Study investigators and study sites

Name	Study site
Takashi Onozuka	Kojinkai Asanuma Hifuka Clinic, Hokkaido, Japan
Hideyasu Takata	Sanrui Hifuka, Saitama, Japan
Nobuhiro Fujita	Sumire Dermatology Clinic, Tokyo, Japan
Meiko Tsunoda	Tsunoda Clinic, Tokyo, Japan
Masanori Hagiwara	Toyosu ParkCity Skin Clinic, Tokyo, Japan
Hiroto Kitahara	Keireikai Kitahara Dermatological Clinic, Tokyo, Japan
Yoko Todoroki	Todoroki Dermatology Clinic, Tokyo, Japan
Koma Matsuo	Nakano Dermatology Clinic, Tokyo, Japan
Kyoko Kaminishi	Eda Dermatology Clinic, Kanagawa, Japan
Toshiya Asai	Asai Dermatology Clinic, Kanagawa, Japan
WookKang Winnie Huh	Dr. Huh’s Dermatology Clinic, Okayama, Japan
Kenichiro Shirao	Shirao Pediatrics Allergology Clinic, Hiroshima, Japan
Keiji Okubo	Okubo Skin Care and Clinic, Fukuoka, Japan
Juichiro Nakayama/Kazuko Imamura	Jyouzan Hifuka Hinyoukika Clinic, Kumamoto, Japan
Yoshihiko Katahira	Ojinkai Katahira Hifu Hinyoukika Clinic, Kagoshima, Japan
Hiroko Koizumi	Koizumi Clinic of Dermatology, Hokkaido, Japan
Kimiyuki Saito	Pediatric Allergy & Rheumatology Clinic, Chiba, Japan
Haruo Kuroki	Sotobo Children’s Clinic, Chiba, Japan
Yuki Horiuchi	Akihabara Skin Clinic, Tokyo, Japan
Akio Taneda	Taneda Dermatology Clinic, Tokyo, Japan
Nobuchika Saito	Saitoh Medical Clinic for Children and Adult, Tokyo, Japan
Shiomi Kawano	Iidabashi Skin Clinic, Tokyo, Japan
Shuhei Fukuro	Fukurokai Fukuro Dermatology Clinic, Kanagawa, Japan
Akihiko Hirase	Nanwakai Hirase Allergie Children's Clinic, Hyogo, Japan
Hiroshi Taniguchi	Takenaokai Taniguchi Pediatrics Clinic, Hiroshima, Japan
Tetsuo Matsuda	Matsuda Dermatology Clinic, Fukuoka, Japan
Chiho Tatsumoto	Aozora Children’s Hospital, Kagoshima, Japan
Hideki Fujita/ Tadashi Terui	Nihon University Itabashi Hospital, Tokyo, Japan
Atsuyuki Igarashi	NTT Medical Center Tokyo, Tokyo, Japan
Shigaku Ikeda	Juntendo University Hospital, Tokyo, Japan
Tomonobu Ito	Tokyo Medical University Hospital, Tokyo, Japan
Yoko Kataoka	Osaka Habikino Medical Center, Osaka, Japan
Kenji Saga	Ario Sapporo Dermatology Clinic, Hokkaido, Japan
Naoko Motohashi	Akemi Dermatology Clinic, Chiba, Japan
Hidetoshi Takahashi	Takagi Dermatological Clinic, Hokkaido, Japan
Yoshio Takasaki	Takasaki Pediatric Clinic, Fukuoka, Japan
Mieko Hata	Takano Medical Clinic, Tokyo, Japan

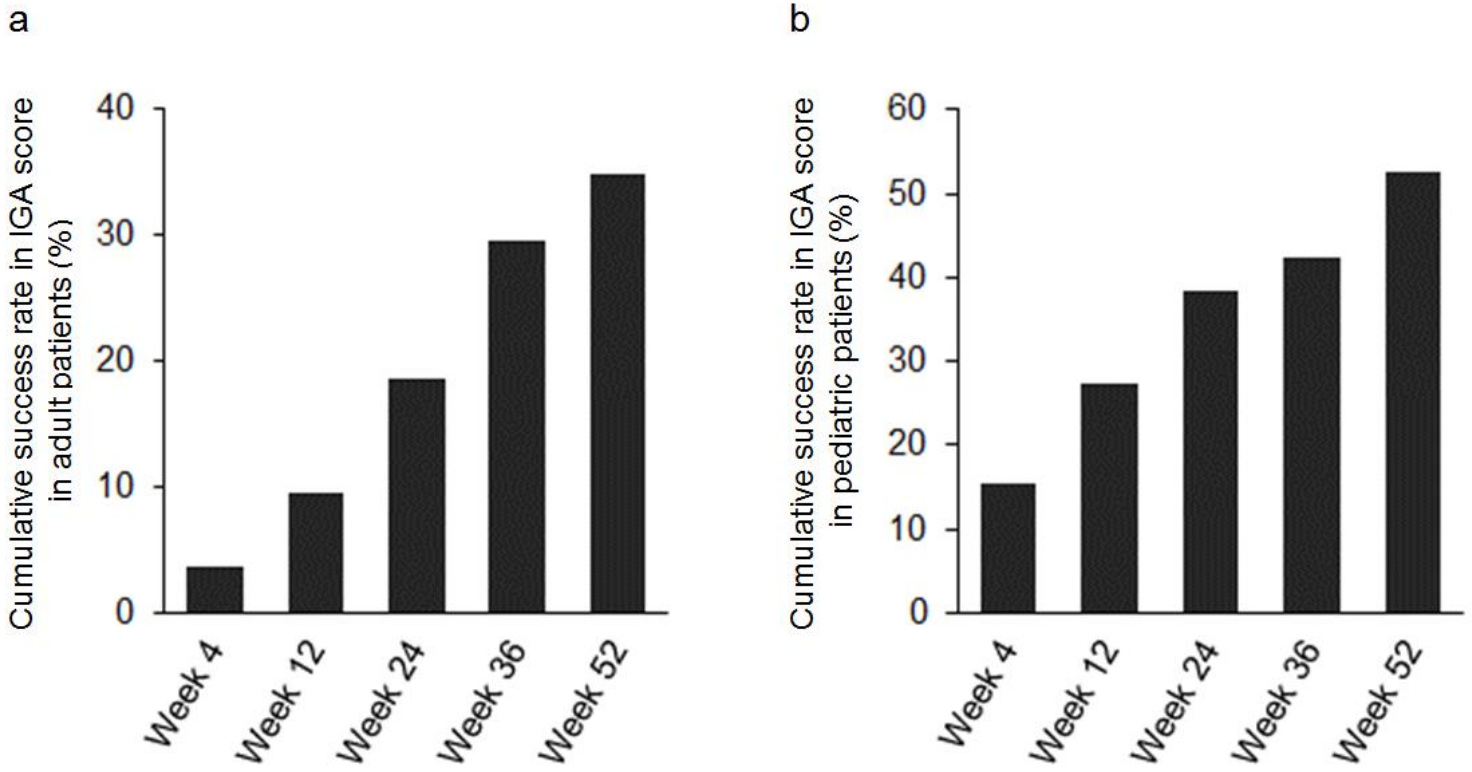

Fig. S1 Cumulative success rate in Investigator's Global Assessment (IGA) score (a) in adult patients (*n* = 166) and (b) in pediatric patients (*n* = 200). The data represent the cumulative percentage of patients achieving an IGA score of 0 or 1 with an improvement of at least two grades

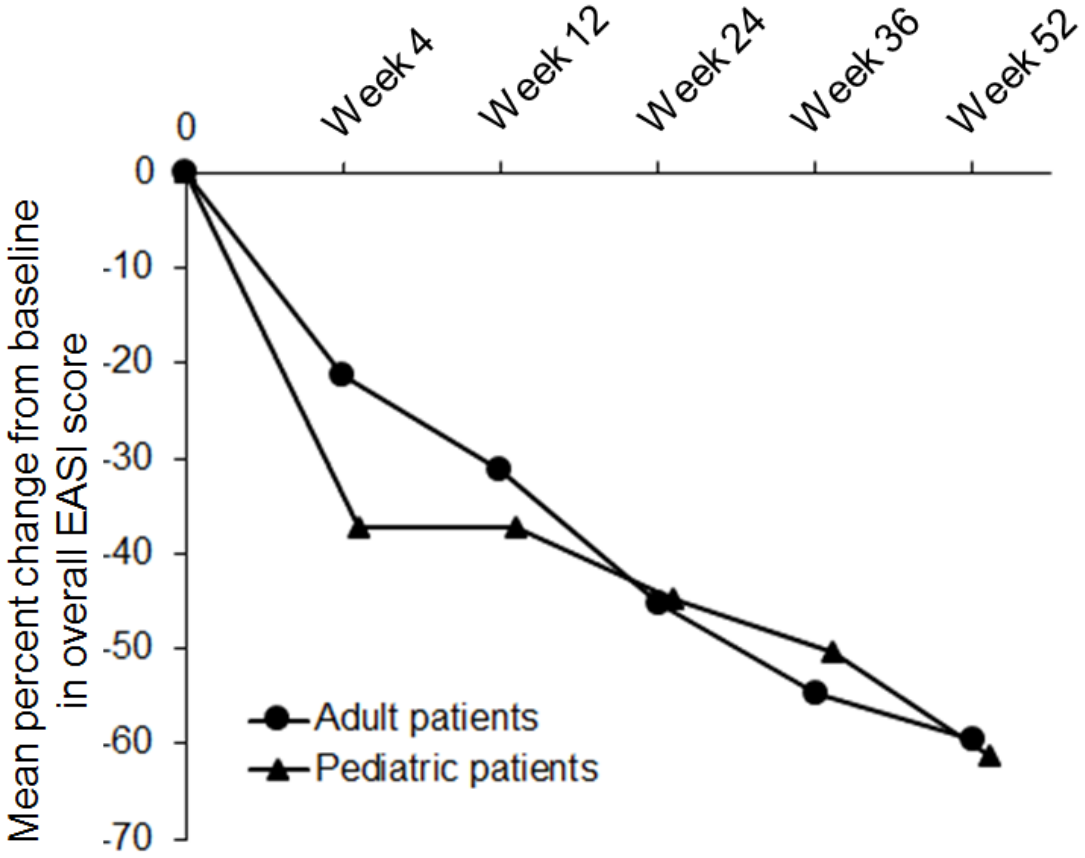

Fig. S2 Mean percent change in overall Eczema Area and Severity Index (EASI) score from baseline at each time point.

Number of adult and pediatric patients, respectively: 158 and 196 at week 4; 147 and 190 at week 12; 133 and 181 at week 24; 128 and 179 at week 36; 123 and 177 at week 52