Clinical Study Report

Title:	A Randomised, Double-Blind, Placebo-controlled, 32-week, Phase IIa trial to investigate the efficacy of OM-85 versus matched placebo in reducing disease severity in children aged 3 to 24 months with early clinical diagnosis of moderate atopic dermatitis
Clinical Protocol Number:	BV-2021/06
Name of Product:	OM-85
Development Phase of Study:	Phase IIa
Indication Studied:	Moderate atopic dermatitis (AD)
Date of First Patient First Visit:	20 December 2021
Date of Last Patient Last Visit:	06 September 2023
Early Study Termination Decision Date:	13 July 2023
EudraCT Number:	2021-003179-33
Sponsor Contact:	Lorenz Lehr Head of Clinical Development
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Co-ordinating Investigator:	PPD

GCP Statement:	This study was conducted in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.
Date of Final Synopsis:	05 January 2024
Date Previous CSRs	Not applicable

2. Synopsis

Name of Sponsor:	OM Pharma SA
Name of Finished Product:	OM-85 (Broncho-Vaxom®)
Name of Active Ingredient(s):	Lyophilised bacterial extract
Individual Study Table Referring to Part of the Dossier:	Volume: Not applicable Page: Not applicable
Study Title:	A Randomised, Double-Blind, Placebo-controlled, 32-week, Phase IIa trial to investigate the efficacy of OM-85 versus matched placebo in reducing disease severity in children aged 3 to 24 months with early clinical diagnosis of moderate atopic dermatitis
Investigators and Study Centres:	Multicentre: this study was conducted at 21 sites. Patients were screened and randomised in Germany, France, Poland, and the Netherlands.
Publication (reference):	Not applicable
Studied Period:	From 20 December 2021 to 06 September 2023
Phase of Development:	IIa
Objectives:	Primary Objective: • To assess the efficacy of OM-85 versus matched placebo in children with moderate atopic dermatitis (AD) in reducing disease severity over the first 16 weeks and the first 24 weeks of the treatment period. Secondary Objectives: • To assess the efficacy of OM-85 versus matched placebo in reducing flares over the treatment period and up to the end of the observational period. • To assess the efficacy of OM-85 versus matched placebo in reducing disease severity up to the end of the observational period. • To evaluate the efficacy of OM-85 versus matched placebo in reducing the use of co-medications for the treatment of AD. • To assess the efficacy of OM-85 versus matched placebo in reducing respiratory tract infections (RTIs) and wheezing episodes over the treatment period and up to the end of the observational period. Exploratory Objectives: • To explore the immunomodulatory effects of OM-85 versus matched placebo at the skin and systemic level. • To evaluate skin lesions and skin/gut microbiomes, incl. skin S. aureus infections. • To assess potential correlations between gut / skin microbiomes and primary and/or secondary outcomes (e.g., Eczema Area and Severity Index (EASI), SCORing AD (SCORAD), Validated

	Investigator's Global Assessment scale for Atopic Dermatitis (vIGA-AD)). • To explore potential correlations between gut microbiome and skin microbiome. • To assess the effect of OM-85 versus matched placebo on allergic sensitisation. <u>Safety Objectives</u>: • To assess the safety of OM-85 versus matched placebo in early moderate paediatric AD.
Methodology:	This was a multicentre, randomised, double-blind, placebo-controlled, exploratory Phase IIa trial to assess the efficacy and safety of daily OM-85 administration in children aged 3 to 24 months with early moderate AD. Patients who met the eligibility criteria were randomised at a 1:1 ratio to receive either OM-85 or the matched placebo. Randomisation was stratified by age (≤12 months versus >12 months) and disease severity at baseline (EASI <16 versus ≥16). The treatment period was 24 consecutive weeks, followed by an 8-week observational period without investigational medicinal product (IMP) treatment. During the first 4 weeks of trial treatment (induction phase) standardised topical corticosteroids (TCS) were applied following a specific dosing scheme. During the next 20 weeks of the treatment period (maintenance phase) and during the observational period the patients could receive TCS as rescue medication after consultation with the Investigator in case of AD flares or if, in the opinion of the Investigator, other medical reasons were documented. A non-binding futility analysis and an efficacy interim analysis was performed as planned once 44 study patients had their primary endpoint of weekly AUC at week 16 observed.
Number of Patients (Planned and Analysed):	Planned: 120 Screened: 76 Randomised: 63 Analysed: OM-85 / Placebo / Total Full Analysis Set (FAS): 30 / 31 / 61 Per-Protocol Set (PPS): 19 / 20 / 39 Safety Analysis Set (SAS): 30 / 33 / 63
Diagnosis and Main Criteria for Inclusion:	Patients enrolled in this study were children aged 3 to 24 months with clinically confirmed early moderate AD. AD onset was to be no longer than 12 months before screening. Moderate severity was defined as a baseline EASI score between 7.1 and 21.0 and lesions covering 30% of the body. Legally authorised representatives (i.e., parent(s) or guardians) of patients provided the appropriate written informed consent before any study-specific procedures were performed.
Test Product, Dose and Mode of Administration, Batch Number:	OM-85 capsules containing 3.5 mg of lyophilised bacterial extract, administered orally once daily during the 24 weeks of the treatment

	period (total of 168 capsules per patient). Batch number: 2100380.
Duration of Treatment:	Patients in each arm were scheduled to receive OM-85 or matching placebo for 24 weeks.
Reference Therapy, Dose and Mode of Administration, Batch Number:	Matching placebo capsules, administered orally once daily during the 24 weeks of the treatment period (total of 168 capsules per patient). Batch number: 2200620.
Auxiliary medicinal products (AxMPs):	**Topical corticosteroids (TCS)** Class I for face and diaper area: hydrocortisone (acetate) 1% cream; and class II for trunk and limbs: prednicarbate 0.25% cream • Background medication: during the first 4 weeks of the IMP treatment period (induction phase) TCS were administered following a specific dosing regimen: 1 application daily during 8 days followed by 1 application every 2 days during 8 days and then 1 application every 3 days until Day 24. • Rescue medication: during the next 20 weeks of the treatment period (maintenance phase) and during the observational period patients could receive TCS after consultation with the Investigator in case of AD flares (defined as of EASI increase by 50 % from baseline or in case of EASI score >21.0). Rescue medication could also be prescribed if, in the opinion of the Investigator, other medical reasons were documented. **Standardised emollient (base cream)** Throughout the complete 32-week study duration after randomisation, all children were to receive standardised applications of an emollient (1-2 applications daily).

Criteria for Evaluation:	Efficacy: **Primary endpoints:** • Weekly area under the curve (AUC) of the EASI score from baseline up to the latest evaluable assessment before or on week 16 visit, use of rescue medication, loss to follow-up or withdrawal of consent, whichever occurs first. • Weekly AUC of the EASI score from baseline up to the latest evaluable assessment before or on week 24 visit, use of rescue medication, loss to follow-up or withdrawal of consent, whichever occurs first. **Secondary Endpoints:** • Time to first new AD flare, defined as ≥ 50% worsening of baseline EASI score or EASI score of > 21.0 (severe AD) from baseline to end of the treatment period and the observational period. • Percentage of patients free of flares from baseline to the end of treatment period. • Difference in free of flares days between treatment groups (placebo versus verum) from baseline to the end of treatment period. • Number of new AD flares during the induction and maintenance period and during whole treatment and observational period. • Weekly AUC of the EASI score from baseline to the end of the treatment period. • Weekly AUC of the EASI score from baseline to the end of the observational period. • EASI score change during the induction and maintenance period and during the whole treatment period and the observational period. • SCORAD score change during the induction and maintenance period and during the whole treatment period and the observational period. • vIGA-AD score change during the induction and maintenance period and during the whole treatment period and the observational period. • Atopic Dermatitis Control Tool (ADCT) score change during the induction and maintenance period and during the whole treatment period and the observational period. • Number and duration in days of topical corticosteroids (TCS) treatments for acute flares during the induction and maintenance period and during the whole treatment period and the observational period. • Incidence of skin infections requiring systemic treatment and antibiotics during the induction and maintenance period and during the whole treatment period and the observational period. • Number of RTI and wheezing episodes during the induction and maintenance period and during the whole treatment period and

during the observational period.

Exploratory Endpoints:

- Change of gut microbiome from baseline to the end of the treatment period and of the observational period.
- Change of skin microbiome during the induction and maintenance period and during the whole treatment period and of the observational period, incl. S. aureus infections.
- Potential correlations between gut microbiome data and primary and/or secondary outcomes (e.g., EASI, SCORAD, vIGA-AD).
- Potential correlations between skin microbiome data and primary and/or secondary outcomes (e.g., EASI, SCORAD, vIGA-AD).
- Potential correlations between gut microbiome data and skin microbiome data (using diversity measures for the skin microbiome).
- Optional exploratory endpoint: change of total immunoglobulin E (IgE) and specific IgEs from baseline to the end of the treatment period and of the observational period.
- Optional exploratory endpoint: change in expression of selected disease biomarkers in blood from baseline to the end of the treatment period.

<u>Safety:</u>

- Incidence of treatment-emergent adverse events and treatment-emergent serious adverse events from baseline to the end of the observational period.

Statistical Method:	<u>Statistical analysis</u>: The primary endpoints were analysed using a linear model with treatment and stratification factor (age ≤12 months versus >12 months) and baseline EASI score as covariates. Least squares mean (LS mean), standard error (SE) and 95% confidence interval (95% CI) were presented at each timepoint for each treatment group. Difference in LS means at 16 and 24 weeks was presented, together with SE, 95% CI and p-value. To maintain the study wise one-sided Type 1 error rate, alpha was fixed to 2.5%. Due to the presence of an interim analysis, alpha was split into two parts to be spent for each data look: a) interim analysis- once 40% information rate for weekly AUC of the EASI score at week 16 had been achieved b) final analysis. Significance levels to be used for the hypothesis testing at each data look was based on O'Brien & Fleming type α-spending method. Furthermore, to test for co-primary endpoints, weekly AUC at week 16 and weekly AUC at week 24, a graphical testing approach was applied for alpha spending. For the hypothesis testing for (1) the weekly AUC of the EASI score at week 16, and (2) the weekly AUC of the EASI score at week 24, in case of rejection of one null hypothesis, the full fraction of the local significance level would be inherited for the other hypothesis testing. For secondary endpoints, all secondary analyses were summarised descriptively by treatment and timepoint for FAS and PPS using the observed data for scheduled visits only, unless otherwise stated. Stratified log-rank tests and Kaplan-Meier plots were used for the analysis of time-to-event endpoints. Change from baseline scores were analysed with mixed model repeated measures (MMRM) model which was fitted including all score data collected at scheduled visits and with treatment group, stratification age group (strata 1), and baseline score as covariates. For final analysis, the type I error was controlled using a fixed-sequence method for secondary endpoints using the order of the endpoints. If both co-primary endpoints were significant, then the first secondary endpoint could be tested using two-sided test and alpha < 0.05. For patients who discontinued the study, the efficacy data captured at the early termination visit were re-assigned to the nearest protocol scheduled time point. <u>Analysis populations:</u> Efficacy endpoints were analysed both on the FAS and the PPS. Safety endpoints were analysed on the SAS.
Summary of Results:	<u>Demographics and baseline disease characteristics:</u> Patient demographics and baseline disease characteristics were similar between the 2 treatment groups. Patients ranged in age from 3 to 23 months (mean 11.9 months). Over half of patients (57.4%) were in the age cohort of ≤12 months, with 16.4% of the patients being between 3 and 6 months old. Most patients were male (65.6%) and almost all patients were white (83.6%). The mean EASI score was 9.73 (standard

deviation (SD): 3.01), the mean SCORAD index was 39.0 (SD: 9.85), and the mean body surface area (BSA) was 20.0% (SD: 9.19). Most patients (63.9%) had a moderate AD severity as assessed by vIGA.

The majority of patients (60.7%) reported at least one major protocol deviation.

Efficacy:

Co-primary endpoints

In the FAS, there was no significant difference between the OM-85 and placebo groups in the LS mean (SE) of the weekly AUC of EASI score from baseline to:

- Week 16: 45.581 (4.281) versus 39.210 (4.217); difference in LS mean: 6.371, 95% CI: -5.783, 18.525, p=0.298
- Week 24: 45.008 (4.389) versus 38.344 (4.323); difference in LS mean: 6.665, 95% CI: -5.795, 19.124, p=0.289

In the PPS, the results were consistent with the FAS analyses.

The null hypothesis for the primary endpoint (AUC Week 16) was not rejected. The hierarchical testing strategy therefore means that p-values for other analyses may not be used to draw general conclusions.

Key secondary endpoints

- There was no significant difference in the FAS between the OM-85 and placebo groups in the LS mean (SE) weekly AUC of EASI score from baseline to the end of the:
    - Treatment period: 37.020 (4.496) versus 35.004 (4.429); difference in LS mean: 2.016, 95% CI: -10.748, 14.781), p=0.753
    - Observational period: 35.681 (4.563) versus 33.394 (4.495); difference in LS mean: 2.287, 95% CI: -10.669, 15.243, p=0.725

  Results were similar in the PPS.
- The change from baseline in EASI score during the induction and maintenance period and during the whole treatment period and the observational period in the FAS was similar between the OM-85 and placebo groups, with a mean (SD) decrease in EASI score of -4.25 (4.409) in the OM-85 group and -5.37 (5.364) in the placebo group after the induction period, and a gradual further decrease until the end of the observational period. There was no significant difference in mean change from baseline in EASI score between treatment groups at the end of the treatment period (difference in LS mean: 0.803, 95% CI: -1.630, 3.235, p=0.517), nor at the end of the observational period (difference in LS mean: 0.292, 95%CI: -2.204, 2.788, p=0.818). Results were similar in the PPS.
- The change from baseline in SCORAD score during the induction and maintenance period and during the whole treatment period and the observational period in the FAS was similar between the OM-

85 and placebo groups, with a mean (SD) decrease in SCORAD score of -9.5 (14.88) in the OM-85 group and -13.4 (13.35) in the placebo group after the induction period. Further decreases in SCORAD score were less marked and a plateau was seemingly reached for both treatment groups from week 20 onwards. There was no significant difference in mean change from baseline in SCORAD score between treatment groups at the end of the treatment period (difference in LS mean: 1.157, 95% CI: -7.364, 9.678, p=0.789) nor at the end of the observational period (difference in LS mean: 1.682, 95% CI: -7.063, 10.428, p=0.705). Results were similar in the PPS.

- The change from baseline in vIGA-AD score during the induction and maintenance period and during the whole treatment period and the observational period in the FAS was similar between the OM-85 and placebo groups. The mean (SD) change from baseline was the most pronounced after the induction period (-0.7 (0.92) for OM-85 and -0.6 (0.73) for placebo) and remained relatively stable across study visits. There was no significant difference in mean change from baseline in vIGA-AD score between treatment groups at the end of the treatment period (difference in LS mean: -0.101, 95% CI: -0.653, 0.450, p=0.718) nor at the end of the observational period (difference in LS mean: -0.013, 95% CI: -0.579, 0.553, p=0.965). Results were similar in the PPS.

<u>Safety:</u>

- The vast majority of patients in the SAS had at least 1 treatment-emergent adverse event (TEAE), with similar proportions between the OM-85 and placebo groups (96.7% and 93.9%). The most frequently reported system organ classes were Infections and infestations, and Skin and subcutaneous tissue disorders.
- TEAEs related to the study treatment were reported in 4 (13.3%) patients of the OM-85 group and 5 (15.2%) patients of the placebo group. The most frequently reported event was worsening of AD. None of the related TEAEs was severe or serious, but they led to study treatment interruption/discontinuation in 2 patients. The study treatment discontinuation was due to worsening of AD.
- Severe TEAEs and serious TEAEs were reported with low frequency in the OM-85 and the placebo groups:
    - Severe TEAEs – 2 (6.7%) patients in the OM-85 group, and 1 (3.0%) patient in the placebo group,
    - Serious TEAEs – 2 (6.7%) patients in the OM-85 group, and 1 (3.0%) patient in the placebo group.
- No TEAE leading to death was reported in either treatment group.
- Most reported TEAEs were mild to moderate in intensity, transient and short in duration, and reported with similar frequency in both treatment groups.
- The 2 patients with a severe TEAE in the OM-85 group were between 3 and 6 months, and the one in the placebo group between 6 and 12 months, but the TEAEs were not considered to be related

	to the study treatment. • None of the patients from age groups 3-6 months and 6-12 months presented a serious TEAE in either treatment group. <u>Exploratory analyses</u> Exploratory endpoints were not assessed due to early termination of the study and low number of available samples.
Conclusions:	The study was prematurely terminated for futility after interim analysis. The study did not achieve its primary objective of efficacy of OM-85 versus matched placebo in reducing disease severity over the first 16 weeks and the first 24 weeks of the treatment period. Due to the limited sample size, along with TCS being used more frequently than initially anticipated, particularly based on the opinion of the Investigator for other medical reasons than for the protocol definition of AD flare, the efficacy of OM-85 on disease severity could not be assessed as planned. The study confirmed the good safety profile of OM-85 in the study population, including in the subgroups of patients between 3-6 months and 6-12 months old.
Final Synopsis Date:	05 January 2024