Protocol Number: D3461C00009

Official Title: A Multicentre, Randomised, Double-blind, Placebo-Controlled Phase 3 Extension Study to Characterise the Long-term Safety and Tolerability of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus

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Clinical Study Report	
Drug Substance	Anifrolumab (MEDI 546)
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A Multicentre, Randomised, Double-blind, Placebo-Controlled Phase III Extension Study to Characterise the Long-term Safety and Tolerability of Anifrolumab in Adult Patients with Active Systemic Lupus Erythematosus

Study dates:
First patient enrolled: 30 June 2016
Last patient last visit: 21 December 2021
The analyses presented in this report are based on a clinical data lock date of 09 May 2022

Phase of development:
Therapeutic confirmatory (III)

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Sponsor's Responsible Medical Officer:
[redacted]

An interim study report based on an interim data analysis from a data cut-off date of 19 March 2020 was published on 20 November 2020.

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

Study centre(s)

This study was conducted at 176 study centres in 24 countries.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

This 3-year Phase III global, placebo-controlled, double-blind long-term extension (LTE) study characterised the long-term safety and tolerability of an intravenous (IV) dosing regimen of anifrolumab 300 mg versus placebo in adult patients with moderate to severe SLE despite standard therapy who had completed treatment in either study D3461C00004 (hereafter referred to as study 04) or D3461C00005 (hereafter referred to as study 05). The primary safety [redacted] are described in the table below.

Table S1 Objectives and Endpoints

Objectives	Outcome Measures
Primary	
To characterise the long-term safety and tolerability of intravenous anifrolumab	• Rates of AESIs and SAEs
[redacted]	

Table S1 Objectives and Endpoints

[redacted]	[redacted]

Study design

This was a 3-year Phase III, global, multi-centre, randomised, double-blind, placebo-controlled, long-term extension (LTE) study, characterising the long-term safety and tolerability of anifrolumab 300 mg administered as IV monthly infusions versus placebo in patients with moderate to severe active SLE despite standard therapy.

Treatment assignment in study 09 followed an Interactive Voice/Web Response System algorithm as follows:

- Patients previously treated with anifrolumab 300 mg continued on blinded anifrolumab 300 mg
- Patients previously treated with anifrolumab 150 mg switched to blinded anifrolumab 300 mg
- Patients previously randomised to placebo were re-randomised 1:1 to blinded anifrolumab 300 mg or placebo

This resulted in an approximate ratio of anifrolumab 300 mg versus placebo of 4:1 in the LTE study.

Target population and sample size

The LTE target population was comprised of patients who had completed the 52-week double-blind treatment period in one of the Phase III studies (study 04 or study 05), met all LTE eligibility criteria and were willing to continue into the extension study.

In the LTE study, patients remained on background standard of care SLE therapy, but investigators were allowed to make adjustments as clinically indicated for disease control throughout the 3-year LTE. Thus, during LTE patients were allowed to change dose, add or switch to a new immunosuppressant. In contrast to study 04 and study 05, there was no requirement of [redacted]. Similar to study 04 and 05, certain SLE medications such as cyclophosphamide, biologics, IV immunoglobulin and IV steroids were prohibited in LTE to protect the safety of participating patients.

The LTE sample size was not based on statistical considerations but was instead defined by all patients completing the double-blind treatment period in studies 04 or 05 and who met all eligibility criteria for study 09 and consented to continue into LTE.

Investigational product dosage, mode of administration and batch numbers

Investigational product (IP) was administered as an IV infusion via an infusion pump over a minimum of 30 minutes. Patients received a fixed dose of 300 mg anifrolumab or placebo once every 4 weeks (Q4W) for a total of 39 doses in LTE. The batch numbers used are listed below.

Study Treatments

Investigational product	Dosage form and strength	Manufacturer	Batch numbers
Anifrolumab (MEDI-546)	150 mg/mL solution of anifrolumab (clear colourless to slightly yellow) intended for IV administration following dilution into 0.9% saline	MedImmune, LLC	**1.00 mL vial:** FC0004/L004168 FN0004/L004168 L004168/FN0004 L005223/FT0089 **2.00 mL vial:** KJ0140 / L010467 KJ0140/L010467 L010467/KJ0140
Placebo	Solution (clear) intended for IV administration following dilution into 0.9% saline	MedImmune, LLC	**1.00 mL vial** JM0267 / L009187 JM0267/L009187 L009187/JM0267 **2.00 mL vial** FC0002/L003661 JM0223/L008501 L003661/FC0002 L008501/JM0223

Commercial anifrolumab was introduced during the study (the 2 mL vials).
IV, intravenous; LLC, limited liability company.

Duration of treatment

The LTE study consisted of a 156-week treatment period, after which patients continued in the study for another 8 weeks to complete a 12-week safety follow-up after last dose of IP (given at Week 152).

Statistical methods

Results are presented for LTE only for the combined feeder studies and LTE.

Analysis sets

Full Analysis Sets

The "full analysis set" consists of all patients who were randomised and received at least 1 dose of IP in the Phase III feeder studies (study 04 or study 05). The "full analysis set – LTE study" comprises all patients who were randomised and received at least 1 dose of

investigational product in the LTE study. Patients are analysed according to the Intention-To-Treat principle (ie, as randomised). Patients who withdrew consent to participate in the study are included up to the date of their study termination.

Treatment analysis groups

The main treatment analysis groups for safety assessments of anifrolumab 300 mg versus placebo in LTE study (including data from LTE only) were:

- **LTE anifrolumab 300 mg:** Patients randomised to anifrolumab 300 mg in study 04 or study 05 and continuing on anifrolumab 300 mg in the LTE study
- **LTE placebo:** Patients randomised to placebo in study 04 or 05 and re-randomised to continue on placebo in the LTE study

To ensure comprehensive assessment of rare events, all data from start of feeder study 04 and study 05 and throughout the LTE study were included for these analyses using the following treatment analysis group for comparing anifrolumab and placebo:

- **All anifrolumab:** Patients randomised to anifrolumab 300 mg in study 04 or study 05 and patients receiving anifrolumab 150 mg in study 05 combined with all patients receiving anifrolumab 300 mg in LTE (ie continuing from anifrolumab 300 mg in feeder study, switched from anifrolumab 150 mg or re-randomised from placebo to anifrolumab 300 mg in LTE study)
- **All placebo:** Patients randomised to placebo in study 04 or study 05 using data from start of feeder study up until switch to anifrolumab 300 mg or to end of LTE for patients re-randomised to placebo in LTE, respectively.

The main analysis treatment groups for exploratory efficacy assessments were (based on combined data from feeder studies and LTE:

- **Combined anifrolumab 300 mg:** Patients randomised to anifrolumab 300 mg at start of study 04 or study 05 using data throughout feeder and LTE.
- **Combined placebo:** Patients randomised to placebo at start of study 04 or study 05 who were, or would have been, re-randomised to placebo in LTE.

Analyses

No formal comparisons were planned in this study.

Adverse events are summarised by descriptive statistics and qualitative summaries, exposure-adjusted incidence rates and adjusted cumulative proportions. Differences between treatment groups are presented for serious adverse events (SAEs), adverse events leading to discontinuation (DAEs), deaths, and adverse events of special interest (AESIs) as adjusted

differences in cumulative proportions and risk differences (based on exposure-adjusted incidence rates [EAIRs]), and respective 95% confidence intervals (CIs).

[redacted]

An interim analysis was performed at the conclusion of studies 04 and 05. Treatment allocation in the LTE study became known to the Sponsor and staff and designated contract research organisation (CRO) personnel involved in the statistical analysis. The blind was maintained for investigators, investigational site staff, AstraZeneca study physician and clinical scientist, CRO operational personnel, and for the patients.

Disposition and study population

In total, 547 patients who had completed the 52-week treatment period on IP in study 04 or study 05 were enrolled and received at least 1 dose of IP in the LTE study. Of these, 257 patients treated with anifrolumab 300 mg in the feeder studies continued on anifrolumab 300 mg (LTE anifrolumab 300 mg group). Out of the 223 patients from the feeder studies placebo treatment groups who entered the LTE, 112 patients were re-randomised to continue on placebo (LTE placebo group) and 111 patients were re-randomised to anifrolumab 300 mg. In addition, 67 patients switched from anifrolumab 150 mg in study 05 to anifrolumab 300 mg.

A higher proportion of patients in the LTE anifrolumab 300 mg group (69.3%) completed the LTE study compared with LTE placebo (69.3% and 48.2%, respectively. More patients in the LTE placebo group compared to the LTE anifrolumab 300 mg group discontinued IP due to withdrawal by patient (22.3% versus 11.7%) or due to lack of efficacy (7.1% versus 5.4%). The proportions of patients who discontinued treatment due to AEs were low and comparable between the LTE anifrolumab 300 mg group (7.0%) and LTE placebo group (8.0%).

The exposure during treatment and follow-up in LTE was 683.5 patient-years (PY) in LTE anifrolumab 300 mg group and 250.3 PY in the LTE placebo group. The total anifrolumab exposure to any dose at any time point during feeder or LTE was 1568 patient years.

Patients who continued into the LTE study had similar baseline (at start of study 04 or study 05) demographics and SLE disease characteristics as compared with the overall feeder study patient population (also including patients who did not enrol in LTE). Baseline demographics [redacted] were also overall balanced between LTE treatment groups. [redacted]

[redacted]

Overall, the baseline SLE treatment was similar between patients randomised to the feeder studies and patients who continued in the LTE study and was generally balanced between LTE treatment groups.

The COVID-19 pandemic was declared during the final year of the LTE study. Study data collection continued throughout the pandemic the pre- and post-vaccination periods. Although there were disruptions related to study visits and patients missed doses, there were no major study disruptions due to the pandemic.

Summary of safety and tolerability results

The safety profile of anifrolumab 300 mg treatment for up to 4 years was consistent with that previously reported for 1-year treatment. No new safety concerns emerged during the LTE study.

- Most patients reported at least one AE, with overall similar AE event rates in the LTE anifrolumab 300 mg group and LTE placebo groups. The majority of AEs were nonserious, mild or moderate in intensity, and did not lead to discontinuation of IP.
- The most common AEs by PT (by event rate) in the LTE anifrolumab 300 mg group were nasopharyngitis, urinary tract infection, and upper respiratory tract infection.
- The SAE EAIR was numerically lower in the LTE anifrolumab 300 mg group compared to the LTE placebo group.
- There were 12 AEs with fatal outcome during the combined feeder and LTE study period, 10 in the All anifrolumab group and 2 in the All placebo group.. Nine of these deaths occurred during the LTE (3 in the LTE anifrolumab 300 mg group [EAIR 0.40/100 PY], one in the LTE placebo group [EAIR 0.40/100 PY], 3 patients treated in the LTE anifrolumab 300 mg after placebo [EAIR 1.0/100 PY] and 2 in the LTE anifrolumab 300 mg after anifrolumab 150 mg [EAIR 1.2/100 PY]). One of the deaths in the LTE anifrolumab 300 mg after placebo group occurred before first LTE dose.
- The DAE EAIRs were low and similar in the LTE anifrolumab 300 mg and LTE placebo groups.
- Key findings for protocol-specified AESIs:
  - The event rates of serious non-opportunistic infections were low and comparable between LTE anifrolumab 300 mg and LTE placebo groups. There were no reported opportunistic infections in the LTE anifrolumab 300 mg group.

  - Overall, infusions of anifrolumab were generally well tolerated. Based on all treatment groups in the combined feeder studies and LTE study, there was one AE of anaphylaxis in the feeder studies, from which the patient recovered.
  - The herpes zoster EAIR was numerically higher in the LTE anifrolumab 300 mg group compared to the LTE placebo group. The yearly EAIRs decreased over time in the Combined anifrolumab 300 mg group.
  - There were no AEs of active tuberculosis (TB) in the LTE or in the feeder studies. The EAIR for latent TB was numerically higher in the LTE anifrolumab group compared to the LTE placebo group.
  - The EAIRs for malignancy and major cardiovascular events (MACE) were low and similar between treatment groups, based on all treatment groups in the combined feeder studies and LTE study.
- The EAIRs of AEs and SAEs reported as related to COVID-19 were higher in anifrolumab compared to placebo-treated patients. There were 3 deaths in anifrolumab treated patients reported as related to COVID-19, all of which occurred early in the pandemic before introductions of vaccines or efficacious treatments for severe COVID-19.
- There were no significant safety trends in in clinical laboratory tests, vital signs, electrocardiograms, or physical examinations.

[redacted]

[redacted]

Conclusions

- The overall long-term safety profile of anifrolumab 300 mg treatment (for up to 4 years) remained consistent with the profile observed with up to one year of treatment. No new safety concerns were identified during the LTE study.
- Long-term anifrolumab treatment was well tolerated.

[redacted]