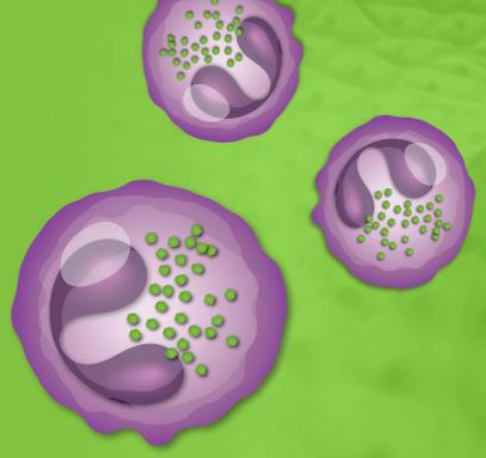
HES Clinical Trial Brief

Phase 3 Pivotal Trial and Open-label Extension



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Mepolizumab Clinical Development Program for Hypereosinophilic Syndrome (HES)

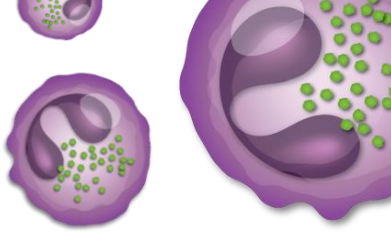
The mepolizumab clinical development program included two phase 3 studies and their respective open-label extension studies (OLEs). This brief outlines the pivotal clinical study, which led to the approval of NUCALA for the treatment of hypereosinophilic syndrome (HES), and its OLE.

NUCALA was approved for use in September 2020 for the treatment of adult and pediatric patients aged ≥12 years with HES for ≥6 months without an identifiable non-hematologic secondary cause.

Clinical Studies of NUCALA in HES

Study (Protocol ID)	Study Title	Trial Phase	Patient Number	Primary Objective
Phase 3 Steroid-Sparing Study (MHE100185)	Multicenter, double-blind, placebo-controlled study to evaluate the corticosteroid-sparing effects of NUCALA in patients with HES and to assess the efficacy and safety of NUCALA in controlling the clinical signs and symptoms of patients with HES. Patients received either IV mepolizumab 750 mg or placebo.	3	85	To evaluate the effects of mepolizumab 750 mg on corticosteroid sparing and the maintenance of clinical stability in patients with disease that requires control with the use of corticosteroids
OLE of Phase 3 Steroid-Sparing Study (MHE100901)	OLE of MHE100185 study to evaluate the safety and efficacy of NUCALA in patients with HES	3	78	To evaluate the long-term safety and efficacy of mepolizumab 750 mg in HES
Phase 3 Pivotal Trial in Prescribing Information (MHE200622)	Randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of NUCALA in adolescent and adult patients with severe HES over 32 weeks	3	108	To demonstrate the efficacy of NUCALA 300 mg subcutaneous compared with placebo based on maintenance of control of HES symptoms during the treatment period
OLE of Phase 3 Pivotal Trial (MHE205203)	Multicenter, 20-week, open-label extension, safety study to describe the long-term clinical experience of NUCALA in patients with HES from Study MHE200622	3	102	To describe the long-term safety profile of NUCALA 300 mg in patients with HES who took part in MHE200622 (phase 3 study)

IV=intravenous; HQ=headquarters.



HES Phase 3 Pivotal Trial Overview

The pivotal trial for NUCALA in patients with HES was a phase 3 study designed to investigate the efficacy and safety of NUCALA 300 mg subcutaneous (SC) once every 4 weeks compared with placebo in adolescent and adult patients with *F1P1L1-PDGFR*α–negative HES. Study methods and efficacy and safety results are presented below and on the following pages.

Key Inclusion and Exclusion Criteria

Key inclusion criteria

- ≥12 years of age
- Diagnosed with HES for ≥6 months
- Blood eosinophil count (BEC) ≥1000 cells/µL at screening
- Had ≥2 HES flares* within past 12 months
- Had ≥4 weeks of stable HES treatment before and including randomization (including but not limited to oral corticosteroid, immunosuppressive, and/or cytotoxic therapies)

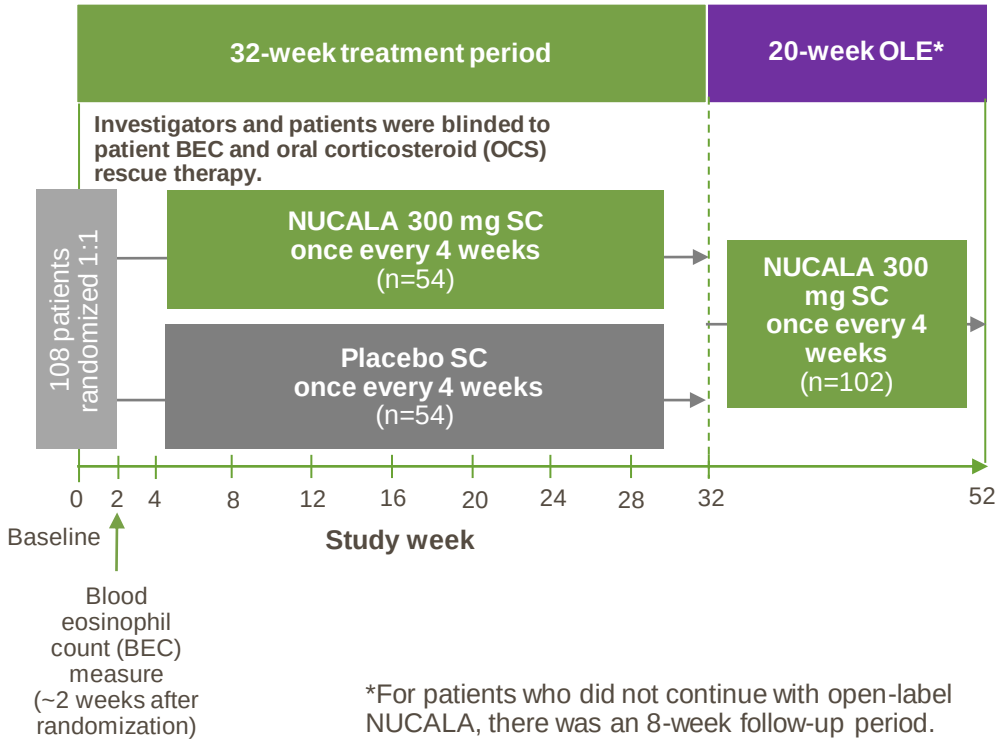
Key exclusion criteria

- Life-threatening HES or life-threatening HES-comorbid disorders
- Eosinophilia of unknown clinical significance
- Positive for *FIP1L1-PDGFR*α fusion tyrosine kinase gene translocation
- History of any clinically significant cardiac damage
- Current malignancy or history of malignancy in remission for less than 12 months prior to randomization
- Chronic or ongoing active and clinically significant infections requiring systemic treatment; pre-existing helminth (worm) infestation in the 6 months before randomization
- Previous NUCALA treatment in the 4 months before randomization
- Any other monoclonal antibodies within 30 days or 5 half-lives of the drug (whichever was longer) of randomization

*Flare is defined as worsening of HES-related clinical symptoms or a BEC requiring treatment escalation; ≥1 flares within the past 12 months must not have been related to a decrease in HES therapy during the 4 weeks before the flare.

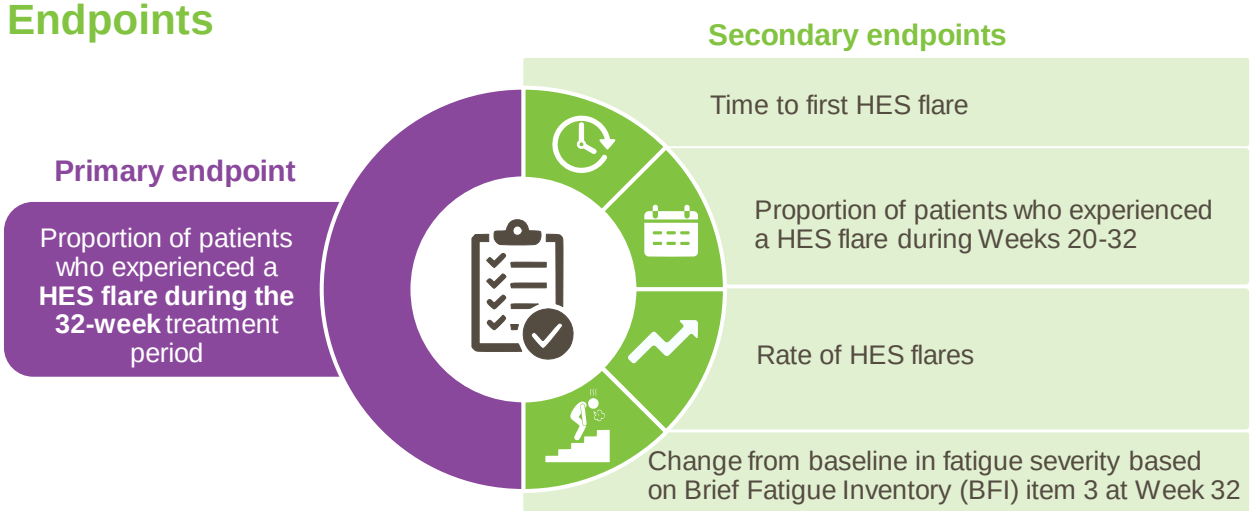
Study Design

- Randomized, placebo-controlled, double-blind, parallel-group, multicenter, phase 3 study
- Patients received NUCALA 300 mg SC or placebo SC once every 4 weeks for 32 weeks while continuing their stable HES therapy



*For patients who did not continue with open-label NUCALA, there was an 8-week follow-up period.

Endpoints



Endpoints (continued)

A HES flare was defined as either:

– A HES-related clinical manifestation based on a physician-documented change in clinical signs or symptoms, resulting in the need for either of the following:

- An **increase in the maintenance OCS dose** by at least 10 mg/d for 5 days or
- An **increase in** or **addition of** any **cytotoxic and/or immunosuppressive HES therapy**

OR,

– Receipt of **≥2 courses** of blinded OCS during the treatment period; an increase in BEC above the predefined threshold level without other clinical manifestations during the study led to administration of blinded OCS treatment for ~2 weeks, after which blood eosinophil count was reassessed

- The Brief Fatigue Inventory (BFI) is a 9-item tool used for rapid assessment of fatigue severity
  - BFI item 3 measures the worst level of fatigue in the past 24 hours using a numeric scale from 0 (no fatigue) to 10 (as bad as you can imagine)
  - Patients in the study completed BFI item 3 daily

Select Baseline Patient Characteristics

Demographics

53%
Female

Mean age
46 years
(range, 12 to 82 years)

Baseline disease characteristics

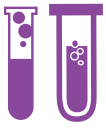
72%
Patients taking **OCS**

67%
Patients taking **≤20 mg/d prednisone or equivalent**

21%
Patients taking **cytotoxic immunosuppressive therapy**

23%
Patients **not** taking chronic OCS or cytotoxic/ immunosuppressive therapy

5.6 years
Duration of HES

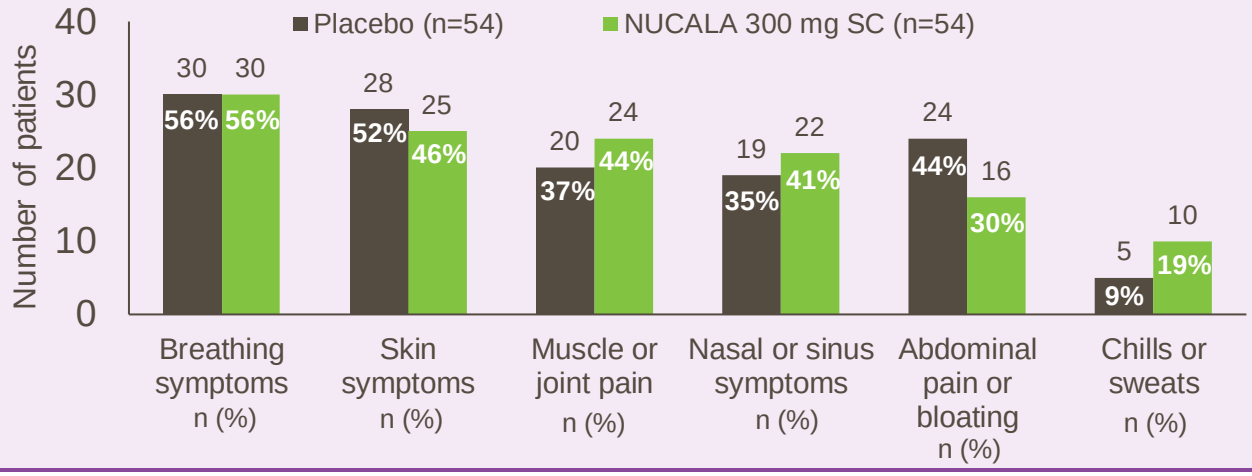


Mean BEC
1350 cells/µL for placebo group
1460 cells/µL for NUCALA group

Most Bothersome HES-related Symptoms

- At baseline, the most bothersome HES-related symptoms across patients were varied
  - Breathing symptoms were the most common symptoms and were reported by **56%** of patients in both treatment groups

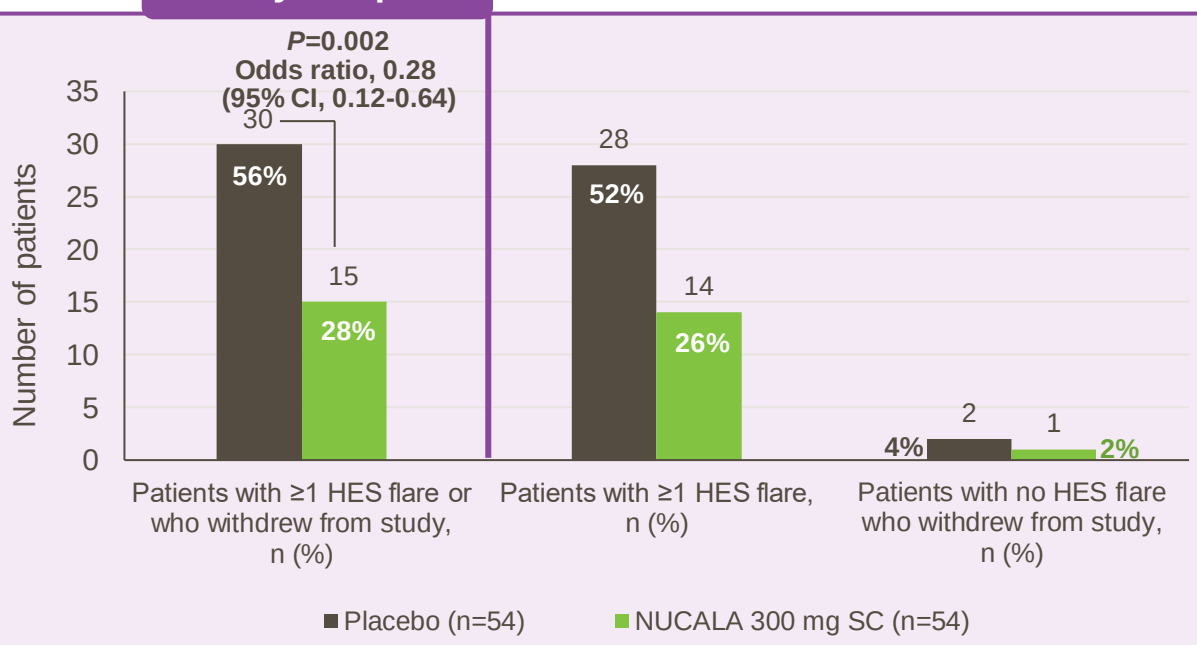
Most Bothersome HES-related Symptoms at Baseline



Primary Efficacy Endpoint

- During the 32-week treatment period, **50%** fewer patients experienced a HES flare or withdrew from the study when treated with NUCALA vs placebo

Primary Endpoint*

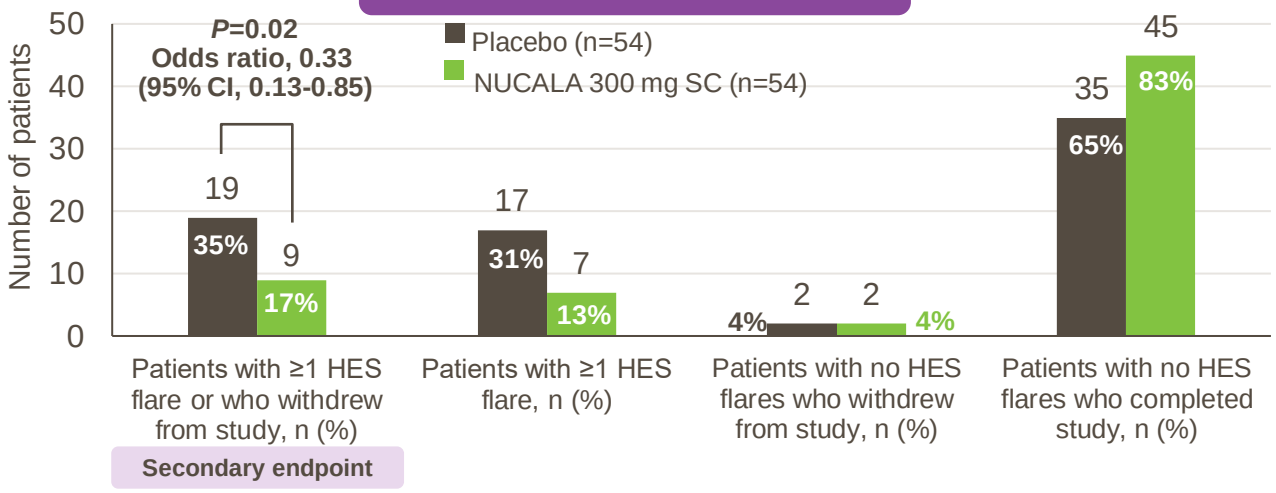


*Analysis compared the number of patients who experienced ≥1 HES flare and/or withdrew from the study prematurely.
CI, confidence interval.

Secondary Efficacy Endpoints

- Secondary endpoints also showed statistically significant improvements in the NUCALA group compared with placebo
  - From Week 20 through Week 32, significantly fewer patients experienced a HES flare or withdrew from the study when treated with NUCALA vs placebo

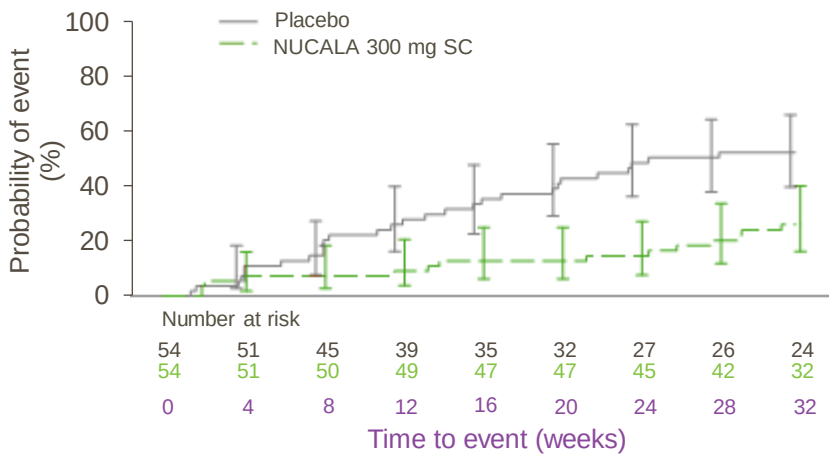
HES Flares Weeks 20-32



Secondary endpoint

- Risk of first HES flare over the treatment period was **66% lower** in NUCALA-treated patients compared with placebo-treated patients

Kaplan-Meier Estimate of the Probability of Having First HES Flare by Time Point



Probability of having HES flare* by 32 weeks:

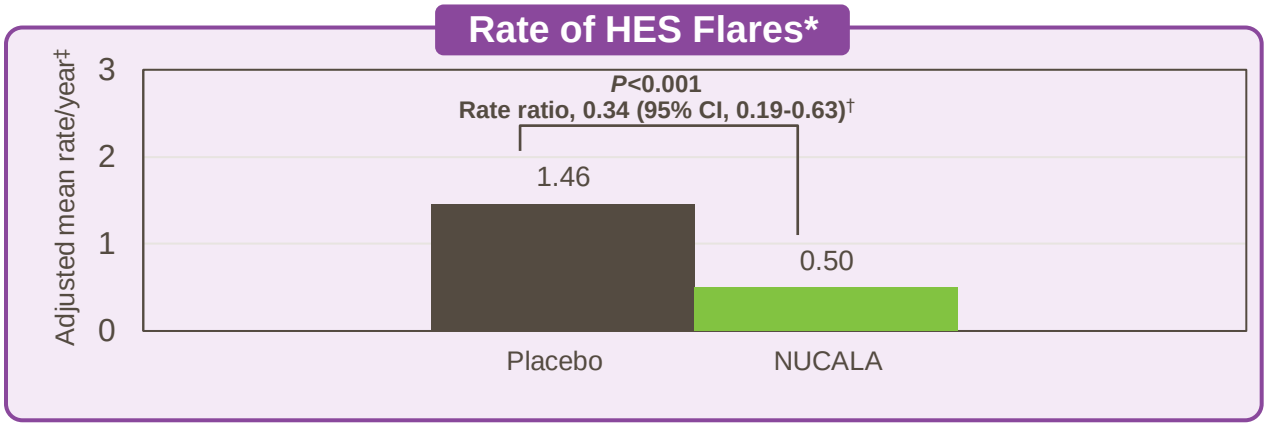
- Placebo, **52.7%** (95% CI, 40.1-66.5)
- NUCALA, **26.3%** (95% CI, 16.5-40.3)

Hazard ratio, 0.34 (95% CI, 0.18-0.67), *P*=0.002

*Log-rank test stratified by baseline OCS (0 to ≤20 mg/d and >20 mg/d prednisone or equivalent) and geographic region.

Secondary Efficacy Endpoints (continued)

– NUCALA resulted in a statistically significant **66% reduction in the annualized rate of HES flares** compared with placebo

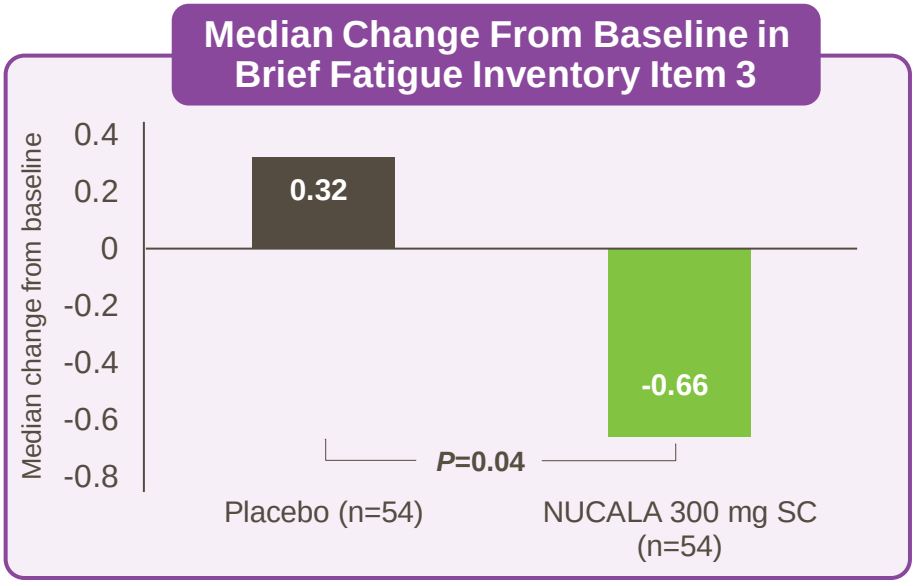


*For patients withdrawing prematurely from the study during the 32-week treatment period, all data up to the time of study withdrawal were used to calculate the rate of HES flares.

†Rate ratio <1 indicates a lower flare rate with NUCALA compared with placebo.

‡Negative binomial model, including baseline OCS dose, geographic region, treatment, and observed time (offset variable).

– NUCALA was associated with a **statistically significant reduction in fatigue severity** vs placebo at Week 32*

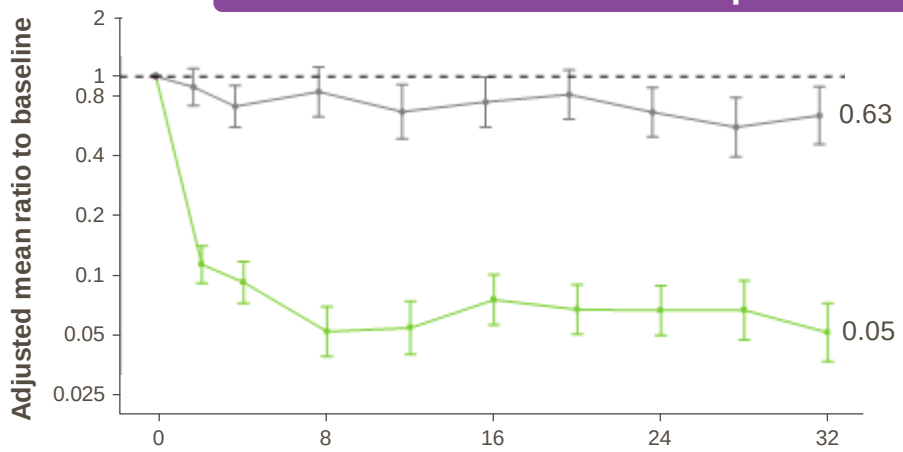


*At baseline, mean Brief Fatigue Inventory (BFI) item 3 scores were similar between treatment groups (4.74 for NUCALA 300 mg; 4.39 for placebo). Higher score indicates worse fatigue severity. For each week of the study, the daily fatigue severity measurements were averaged. Severe fatigue was defined as a baseline BFI item 3 score of ≥7; not severe was defined as a baseline BFI item 3 score of <7.

Pharmacodynamic Results

– At Week 32, patients treated with NUCALA had a 92% reduction in blood eosinophils compared with placebo

Reduction in Blood Eosinophil Counts (BEC)



At **Week 32,** the geometric mean BEC in the **NUCALA** group showed a marked decline from baseline to **70 cells/µL** compared with a slight decline in the placebo group to 900 cells/µL.*

- Placebo
- NUCALA 300 mg SC

*At baseline, geometric mean BEC levels were similar in the NUCALA (1460 cells/µL) and placebo (1350 cells/µL) groups.

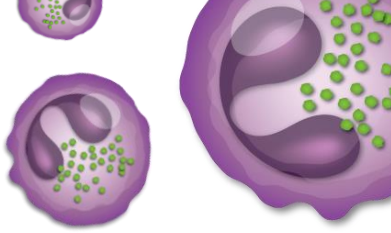
Key Safety Results

- Safety results were consistent with the known profile of NUCALA
- Percentages of patients who experienced treatment-related adverse events (AEs) and serious adverse events (SAEs) in NUCALA and placebo groups were similar

Table 1. Summary of AEs and SAEs

Adverse Event Type	Patients, n (%)	
	Placebo (n=54)	NUCALA 300 mg SC (n=54)
Any Adverse Event (AE)	**47 (87)**	**48 (89)**
AE related to study treatment	7 (13)	12 (22)
Injection-site reaction	2 (4)	4 (7)
AE leading to permanent discontinuation of study treatment	2 (4)	0
AE leading to withdrawal from the study	2 (4)	1 (2)
Any Serious Adverse Event (SAE)	**9 (17)**	**10 (19)**
Fatal SAE	0	1 (2)*
Only SAE reported by ≥1 patient: HES	1 (2)	1 (2)

*The 4 events associated with a single fatality were HES, pneumonia, respiratory failure, and septic shock, none of which were considered related to study treatment by the investigator.



Key Safety Results (continued)

- The most frequent on-treatment AEs were bronchitis, headache, and nasopharyngitis

Table 2. Summary of Most Frequent On-treatment AEs*

Adverse Event (AE)	Patients, n (%)	
	NUCALA 300 mg SC (n=54)	Placebo (n=54)
Bronchitis	8 (15)	10 (19)
Upper respiratory tract infection	8 (15)	2 (4)
Headache	7 (13)	7 (13)
Nasopharyngitis	7 (13)	7 (13)
Pain in extremity	6 (11)	2 (4)
Diarrhea	5 (9)	7 (13)
Rhinitis	5 (9)	6 (11)
Pruritus	4 (7)	7 (13)

*Reported in >10% of the patients in any treatment group.

- In patients with HES receiving 300 mg of NUCALA
  - One patient had detectable anti-NUCALA antibodies
  - No neutralizing antibodies were detected

Clinical Implications of Phase 3 Pivotal Trial

- NUCALA added to standard-of-care therapy significantly reduced the occurrence of HES flares compared with placebo and improved patient symptoms compared with placebo
- Over 32 weeks of NUCALA treatment compared with placebo:
  - **50% fewer** patients experienced a HES flare or who withdrew from study (56% vs 28%; *P*=0.002)
  - Risk of first HES flare over the study period was **66% lower** (hazard ratio, 0.34; 95% CI, 0.18-0.67; *P*=0.002)
  - There was a **66% reduction** in the annualized rate of HES flares (rate ratio, 0.34; 95% CI, 0.19-0.63; *P*<0.001)
  - **Change from baseline in BFI item 3** significantly **improved at Week 32** (*P*=0.036)
- Safety results were consistent with the known profile of NUCALA
  - The **percentage of patients** in the NUCALA and placebo groups who experienced **AEs** were **89% and 87%, respectively**. Serious adverse events occurred in 19% of patients in the NUCALA group and 17% of patients in the placebo group
  - The **most frequently reported AEs** for NUCALA were **bronchitis, rhinitis, headache, nasopharyngitis,** and **pain in extremity**

Open-label Extension Overview

The objective of the OLE of the pivotal trial was to characterize the safety profile and clinical benefit of NUCALA + stable HES therapy* for an additional 20 weeks in patients who completed the phase 3 pivotal trial.

*Existing HES therapy included, but was not limited to, systemic corticosteroids, immunosuppressive therapy, and/or cytotoxic therapy.

Key Inclusion and Exclusion Criteria

Key inclusion criteria

- Patients aged ≥12 years who completed the 32-week phase 3 pivotal trial or had prematurely withdrawn from treatment but continued to be assessed until Week 32
- Treating physician confirmed a positive benefit/risk ratio for NUCALA treatment

Key exclusion criteria

- Hypersensitivity to any monoclonal antibody (including NUCALA)
- Any malignancy development during the phase 3 pivotal trial
- Any clinically significant medical conditions uncontrolled with standard-of-care therapy not associated with HES (eg, unstable liver disease, cardiac damage, ongoing active infectious disease)
- Any patient who discontinued the phase 3 pivotal trial based on liver chemistry stopping criteria

Study Design

n=102

Phase 3, multicenter, open-label extension safety study

20 weeks of treatment*

Patients who completed phase 3 pivotal trial → Patients received NUCALA 300 mg once every 4 weeks for a total of 5 doses during the 20-week treatment period

HES standard-of-care therapy could have been adjusted starting 4 weeks after the first dose of NUCALA, when investigators were unblinded to blood eosinophil levels

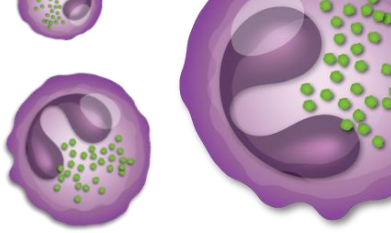
Primary safety endpoints

- Number of patients with AEs (serious and nonserious) up to 28 weeks
- Number of patients with antidrug antibodies up to 28 weeks

Exploratory endpoints (based on efficacy)

- Annualized rate of HES flares†
- Change in mean daily OCS dose from Weeks 0-4 to Weeks 16-20 (in patients receiving OCS during Weeks 0-4)
- Proportion of patients receiving OCS during Weeks 0-4 who achieved a ≥50% reduction in mean daily OCS dose from Weeks 0-4 to Weeks 16-20
- Change from baseline in blood eosinophil count at Week 20

*There was an additional 8-week follow-up period from Weeks 20 to 28.
†HES flare: worsening of clinical signs/symptoms or increased eosinophils, resulting in an escalation/addition of OCS or cytotoxic/immunosuppressive therapy



Clinical Implications of the Open-label Extension Trial

Safety

- The **safety profile** of NUCALA 300 mg administered SC once every 4 weeks for up to 20 weeks was **similar to that observed in the phase 3 pivotal trial**
  - The overall incidence of adverse events was 65%
  - The overall incidence of on-treatment serious adverse events was 8% with infections most common (5%); none led to discontinuation
  - Adverse events leading to study treatment discontinuation or study withdrawal were <1%
  - The most frequent on-treatment AEs (≥5%) were diarrhea (12%), pruritus (7%), headache (6%), vomiting (6%), arthralgia (5%), constipation (5%), nasopharyngitis (5%), nausea (5%), and sinusitis (5%)
  - No deaths were reported, and none of the on-treatment serious adverse events were reported in >1 patient

Immunogenicity

- One patient (who previously received NUCALA in the pivotal trial) had a positive anti-drug antibody result with no neutralizing antibodies at baseline, continued to receive NUCALA, and did not test positive at any subsequent time point

Efficacy

The **clinical benefit of NUCALA as add-on treatment** that was demonstrated in the phase 3 pivotal trial was **maintained for an additional 20 weeks** in the OLE in 102 patients

- Based on **exploratory endpoints**:
  - The **annualized flare rate** in the previous placebo and previous NUCALA groups was 0.37 (0.16-0.86) and 0.14 (0.04-0.49) events/year, respectively
  - In **patients receiving OCS** during Weeks 0-4 (n=72), 28% achieved a ≥50% reduction in mean daily dose during Weeks 16-20
  - The **blood eosinophil count** was reduced by 89% in patients previously receiving placebo and remained reduced for those previously receiving NUCALA at Week 20