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CLINICAL TRIAL OPEN ACCESS

Clinical Trial: Safety and Efficacy of a Novel Oesophageal Delivery System for Topical Corticosteroids Versus Placebo in the Treatment of Eosinophilic Oesophagitis

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ABSTRACT

Background: EsoCap is a thin mucoadhesive film designed to target the oesophageal mucosa. The device loaded with mometasone furoate (ESO-101) is under investigation for the treatment of eosinophilic oesophagitis (EoE).

Aims: To evaluate the efficacy, safety and tolerability of ESO-101 in patients with active EoE.

Methods: We conducted a randomised, placebo-controlled, phase 2, proof-of-concept trial at 14 European sites in adults with EoE. Participants received placebo, uncoated EsoCap ($n=15$), or EsoCap loaded with 800 μg of mometasone furoate ($n=28$) once daily during 28 days. The primary outcome was the absolute change in the peak eosinophil count; secondary outcomes were histologic, clinical and endoscopic measures.

Results: Treatment with ESO-101 resulted in reduction (mean ± SD) of 49.1 ± 88.4 eosinophils/high-power field from baseline, compared with 6.6 ± 65.1 with placebo ($p=0.03$). With ESO-101, 48% and 44% of patients achieved <15 and <6 eosinophils/high-power field, respectively; these were 0% with placebo. EoE Endoscopic Reference Score reduced significantly in patients

treated with ESO-101. In contrast, dysphagia and odynophagia severity decreased similarly in both groups. There were no serious treatment-emergent adverse events. Mean serum cortisol did not change significantly throughout the trial. Notably, no oropharyngeal or oesophageal candidiasis was documented. The device was well tolerated.

Conclusions: ESO-101 was superior to placebo in reducing oesophageal eosinophilia. The device was safe and well tolerated in adults with EoE, supporting the continued development of ESO-101 for the treatment of EoE (Trials.gov No.: NCT04849390; Eu-CT No.: 2020–000082-16).

1 | Introduction

Eosinophilic oesophagitis (EoE) is a chronic inflammatory disease of the oesophagus, characterised by eosinophilic infiltration and upper gastrointestinal symptoms [1, 2]. Standard-of-care treatments for EoE include food elimination diets [3], proton-pump inhibitors (PPIs) [4] and swallowed topical corticosteroids [5]. Recently, a new biological treatment directed against the interleukin-4 receptor alpha has been added to the therapeutic armamentarium for EoE [6]. Oesophageal dilatation is also performed in the case of strictures [7]. The goal of topical therapy with corticosteroids in EoE is to maximise loco-regional efficacy with oesophageal-specific drug delivery and drug formulation, while reducing systemic bioavailability and thus avoiding systemic effects [1]. However, topical corticosteroid therapy in EoE has yielded widely heterogeneous results due the use of different active ingredients and doses, administration methods, formula composition and different volumes [8]. To date, topical forms of budesonide have been approved for EoE [9–12], and historically fluticasone was also used, albeit frequently delivered from an asthma inhaler [10]. In addition, the available data and pharmacological features of mometasone furoate, a different corticosteroid, are promising regarding efficacy in EoE [13–15].

ESO-101 is an innovative, unique pharmaceutical in the form of a thin mucoadhesive film containing mometasone furoate, designed for targeted oesophageal administration of the active substance in the oesophagus [16]. The film enables a long mucosal contact time and maximises the deposition of mometasone furoate, a key goal in EoE. Importantly, the ESO-101 film has no contact with the oral mucosa, but rather delivers the corticosteroid directly to the oesophageal mucosa. Because of minimal enteral absorption of mometasone furoate and because the portion of the mometasone furoate dose absorbed in the gastrointestinal tract undergoes extensive hepatic metabolism, systemic bioavailability is low [17], suggesting the possible of a low rate of systemic side effects [18].

Nevertheless, ESO-101 needed to be tested clinically to demonstrate proof-of-concept. Therefore, the aim of this double-blind, randomised, placebo-controlled trial was to investigate the efficacy, safety and tolerability of mometasone furoate administered via the ESO-101 delivery system.

2 | Methods

2.1 | Study Design

This randomised, double-blind, placebo-controlled, parallel groups, multicentre, phase 2 study was conducted at 14 medical centres in 5 European Countries between 29 Jun 2021 (first patient in) and 09 Oct 2023 (last patient out) to evaluate the safety, tolerability and efficacy of the ESO-101 device once daily (EsoCap AG, Basel, Switzerland) over 28 days in adults with EoE (ClinicalTrials.gov registration NCT04849390; clinicaltrialsregister.eu/Eu-CT No.: 2020–000082-16). The ACESO study design is summarised in Figure 1A.

The study protocol was approved by central Ethic Committees in all participating countries. The study was conducted in accordance with the principles set forth in the Declaration of Helsinki (Fortaleza, Brazil, amendment) and in compliance with International Conference on Harmonisation—Good Clinical Practice standards. No changes were made to the study methods after the start of the trial.

2.2 | Participants

Eligible patients aged between 18 and 70 years, with a confirmed diagnosis of EoE, were considered for participation if they presented with clinico-histologically active disease, defined by (1) a dysphagia or odynophagia severity sore of ≥4 on a 11-point numerical rating scale for ≥1 day during the 7 days before the screening visit (visit V1); and (2) a peak eosinophil count ≥15 eosinophils/high-power field (hpf) at 2 of 3 levels of the oesophagus at the screening endoscopy performed at visit V2, as measured in a total of 6 biopsies (2 each from the proximal, mid and distal segment of the oesophagus). Females of child-bearing potential could not be pregnant or lactating at the time of enrolment and had to use adequate contraception during the study. Written informed consent was obtained from each participant at screening.

Patients were excluded if they met any of the following criteria: history of or active eosinophilic gastroenteritis and/or colitis, inflammatory bowel disease, celiac disease, oral or oesophageal mucosal infection of any kind or oesophageal varices; gastroesophageal reflux disease with Los Angeles Grade B or higher [19], or erosive esophagitis grade 2 or above [20]; presence of Barrett's oesophagus with a maximum length of ≥3 cm with intestinal metaplasia or dysplasia; peptic stricture, achalasia, significant hiatal hernia >3 cm, oesophageal scleroderma or diagnosis of Lichen planus; cirrhosis or portal hypertension; or history of upper gastrointestinal bleeding within 8 weeks before screening. Patients who underwent oesophageal dilation within the previous 8 weeks or who had a high-grade stricture or narrowing where a standard 8–10 mm endoscope could not pass without dilatation at the screening endoscopy were also excluded. Additionally, patients who were unable to swallow a same size test tablet as ESO-101 were not included.

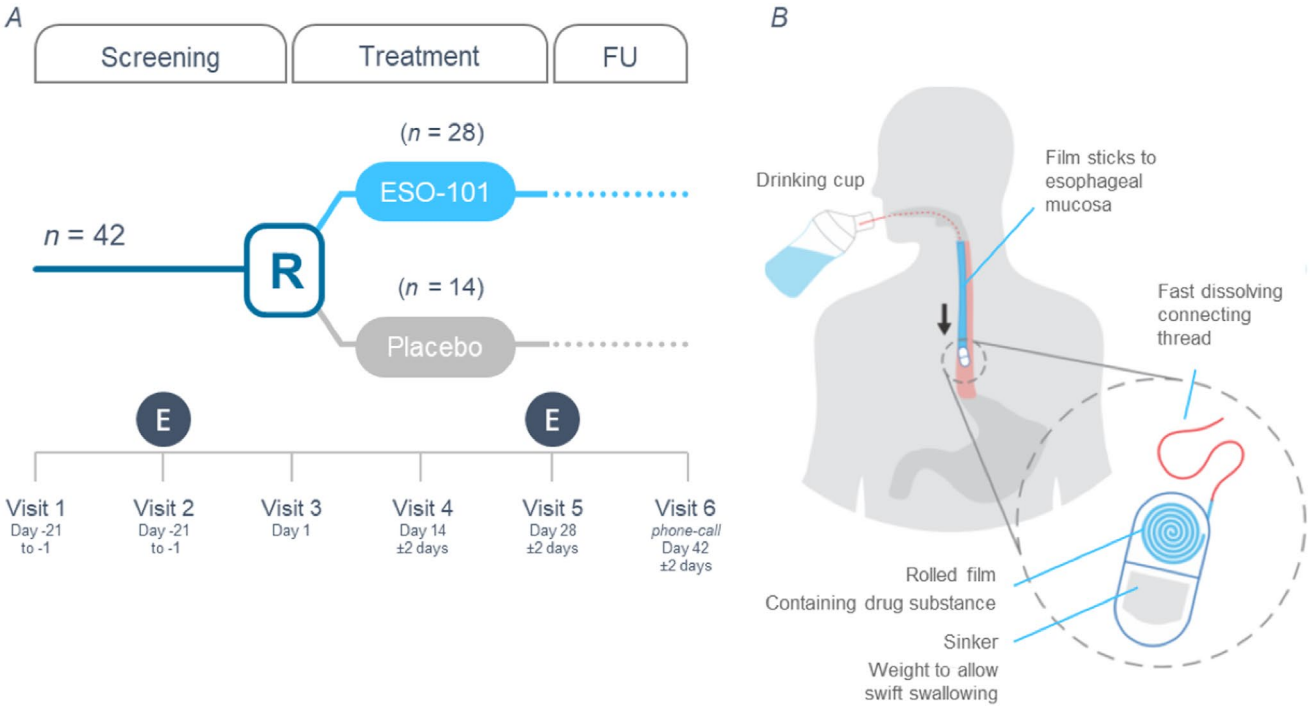

FIGURE 1 | ACESO trial design and EsoCap drug delivery system. (A) Schema of the trial design. This was a double-blind, randomised, placebo-controlled trial to evaluate the efficacy, safety and tolerability of mometasone furoate administered via the EsoCap system. (B) EsoCap system. ESO-101 is a thin, mucoadhesive film loaded with mometasone furoate, allowing for direct delivery and prolonged exposure of the corticosteroid to the oesophageal mucosa. The placebo consisted of the EsoCap system without any active ingredient in the film. Patients administered the treatment once daily for 28 days. E, endoscopy (including biopsy); FU, follow-up; *n*, number of planned patients; *R*, randomisation.

The use of systemic corticosteroids, immunosuppressant or biological therapy within 3 months before the screening endoscopy, topical, inhaled or intranasal corticosteroids during the 4 weeks prior to enrolment until the end of treatment (EoT), or the use of systemic leukotriene receptor antagonists or chronic oral or systemic anticoagulants from 2 weeks before Screening (V1) until EoT was prohibited. Changes in PPI dosing regimen and the initiation of a diet-modifying food restriction within 4 weeks before the screening endoscopy until EoT were additional exclusionary criteria.

Participants were allowed to continue PPI therapy if they had a stable PPI dose for at least 30 days prior to study enrolment. Antihistamines were permitted.

2.3 | Intervention and Randomisation

A detailed description of the ESO-101 drug delivery system was previously published [16, 21]. Briefly, it consists of a mucoadhesive, thin polymer film that is rolled up and inserted into a commercially available but slotted hard gelatine capsule (Figure 1B). The free end of the film that protrudes from the capsule is connected to a thread called a retainer, which is responsible for the exact delivery of the system as a trigger mechanism. There is also a weight inside the capsule to facilitate the swallowing process. The capsule with the film is placed in a special applicator, to which the free end of the retainer is attached. The applicator, which resembles a beak cup, is filled with water so that when the device is taken, the capsule falls out of the applicator into the patient's throat, where it is swallowed together with the water. Once the retainer is expanded to the maximum, the film is pulled out of the capsule during transport through the oesophagus and placed there. Afterwards, the film begins to dissolve and forms a mucoadhesive gel, from which the drug can be easily released.

Patients were randomised by an interactive web response system (IWRS) with a fixed block size of 3 with 2:1 randomisation (ESO-101:placebo). No stratification was applied. Patients received either ESO-101 dispersible polymer film loaded with 800 μg mometasone furoate rolled inside or matching placebo, which was the ESO-101 drug delivery system with no active ingredient in the film. The duration of treatment was 28 days.

After training with a sample device, participants were given a drinking cup and applicators with ESO-101 active medication or placebo and instructed to administer the treatment once daily in the evening at bedtime and after oral hygiene for 28 days, at which time the outcomes were assessed. Patients were asked not to eat until they awake the next morning and not to drink for at least 2 h after capsule intake.

During the trial, subjects, investigators, the sponsor and all other personnel involved in the conduct of the trial were blinded to the treatment administered. An unblinded statistician generated the randomisation list and provided it to the IWRS provider. One set of emergency envelopes was produced for the Medical Safety department. To maintain the blind, ESO-101 and placebo had identical appearance shape and colour and had identical labelling and packaging. The premature breaking of the code was restricted to emergency cases, in

which knowledge of the administered drug was necessary for adequate treatment. No code was prematurely broken.

2.4 | Outcomes

The primary endpoint was the absolute change in the peak eosinophil count (cells per hpf) from baseline to EoT based on the histologic assessment of oesophageal biopsy samples by one single central reader blinded to patient and visit data. In each analysed biopsy sample, the peak eosinophil count was determined in 3 hpfs.

Secondary endpoints included the proportion of patients with histological remission (e.g., peak eosinophil count in all oesophageal samples <15 eosinophils/hpf at EoT, and with <6 eosinophils/hpf, overall and determined differentially in each of the 3 oesophageal thirds); the proportion of patients with an improvement in the dysphagia and odynophagia severity score, measured with a 0–10 numerical rating scale for either dysphagia or odynophagia, from baseline to EoT. Improvement of symptoms was defined as any reduction of the dysphagia severity score at EoT compared to baseline. The endoscopic response was measured locally by unblinded endoscopists using the eosinophilic esophagitis endoscopic reference score (EREFS) [22] using a 0–9 scale in both the upper and lower oesophageal halves (total score range 0–18). Inflammatory (i.e., scores for oedema, furrows and exudates) and fibrotic (i.e., scores for rings and strictures) EREFS subscores [23] were also evaluated.

The safety and tolerability of ESO-101 were additional endpoints. Treatment-emergent adverse events and serious adverse events and adverse events of special interest (oral, oropharyngeal and oesophageal candidiasis) were documented. Patient-reported treatment satisfaction was assessed using an 11-item questionnaire at the EoT visit.

2.5 | Statistical Analysis

A sample size of 42 participants (28 in the active and 14 in the placebo groups) was calculated on the basis of data results from a previous phase 3 trial involving patients with EoE, assuming a dropout rate of 15% and a power of 80% to detect between-groups absolute mean change from baseline to EoT in the overall peak eosinophil count at a two-sided significance level of 5% using a 2-sample *t*-test, with the 95% confidence interval presented.

Continuous endpoints were described by mean ± standard deviation (SD), median (interquartile range [IQR]) and min and max values. The absolute change in the overall peak eosinophil count from baseline to EoT was analysed using a two-sample t-test. The change in EREFS total score from baseline was analysed using an exact Wilcoxon rank sum test. Categorical endpoints were summarised using frequency counts and percentages per group. A Fisher's exact test was used to test the difference between treatment groups for categorical endpoints. All randomised patients who received at least one dose of investigational medicinal product (IMP), that is, any dose ESO-101 or placebo were analysed in the intention-to-treat analyses set, and all patients of this set without any major protocol deviations regarding the primary efficacy endpoints were analysed additionally in the per-protocol set.

An interim analysis was not performed. All analyses were performed with statistical software SAS version 9.4. A p-value <0.05 was considered to be significant.

3 | Results

3.1 | Demographics and Baseline Characteristics

Of 59 patients screened, 43 met inclusion criteria and were randomised, 28 in the ESO-101 and 15 in the placebo group (Figure 2). 40 patients (27 in the ESO-101 and 13 in the placebo group) completed the double-blind phase (93%), but all 43 patients were evaluable for the primary analysis. Only four major protocol deviations led to an exclusion from the per-protocol set: two for early termination, one for non-compliance with IMP intake and one for incomplete data entry. All patient data were included in the intention-to-treat analysis; the per-protocol analysis included the 39 patients without major protocol deviations. The trial was carried out between 29 June 2021 (first patient in) and 09 October 2023 (last patient out).

The demographic and clinical characteristics of the patients at baseline were similar across trial groups (Table 1). There were 33 males and 10 females, the mean ± SD age being 40.8 ± 12.2 (range 19–65 years). They had had substantial symptom burden (mean ± SD dysphagia and odynophagia scores, 5.7 ± 1.5 and 3.6 ± 2.8, respectively) and had active EoE (mean ± SD peak eosinophil count, 86.2 ± 55.6 eosinophils/hpf). The mean EREFS score was 7.3 ± 2.8. In both treatment groups, the most common medical history was seasonal allergies. Details on previous and concomitant medication are provided in Table S1.

Treatment compliance calculated by investigational medical product accounting achieved 100% in ESO-101 and 93% in the placebo groups.

3.2 | Efficacy

3.2.1 | Primary Endpoint

At the Day 28 EoT visit, peak eosinophil counts decreased from baseline by a mean of 49.1 ± 88.4 eosinophils/hpf in the ESO-101 group and increased by 6.6 ± 65.1 eosinophils/hpf in the placebo group ($p=0.0318$) (Figure 3A). The results were similar in the per-protocol analysis (Table S2).

3.2.2 | Secondary Endpoints

3.2.2.1 | Histologic Outcomes of EoE. Histologic remission defined as <15 eosinophils/hpf at all three oesophageal levels at EoT was achieved in 13 of 27 (48%) in the ESO-101 group but in none (0%) in the placebo group ($p=0.0028$) (Figure 3B).

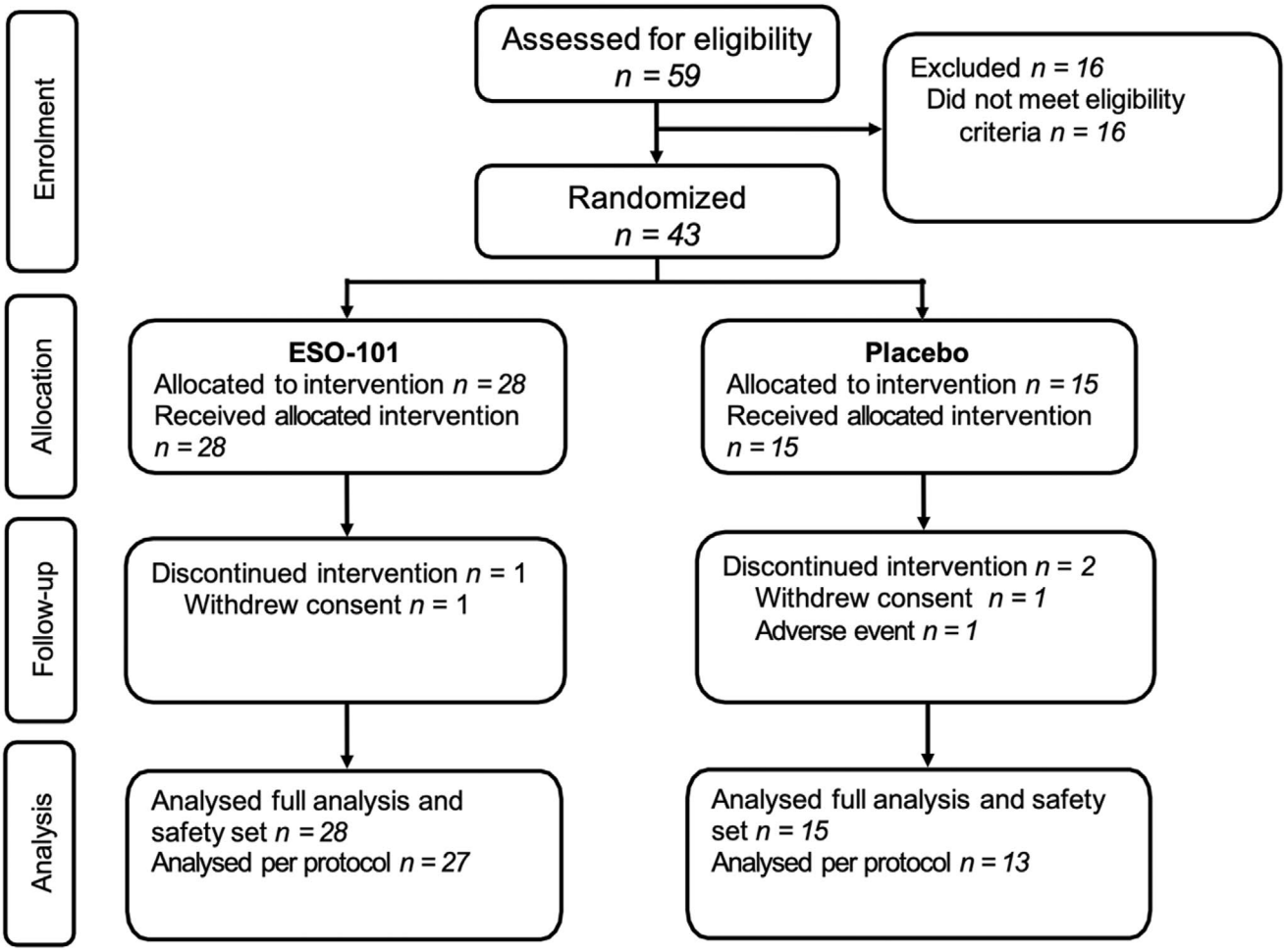

FIGURE 2 | Patient disposition according to the CONSORT flow diagram.

At the <6 eosinophils/hpf threshold, 12 of 27 (44.4%) in the ESO-101 group achieved this endpoint compared to none in placebo ($p = 0.0035$) (Figure 3C).

When histologic remission criteria were assessed per oesophageal segments (Figure 3B,C), higher proportions of patients receiving ESO-101 had <15 or <6 eosinophils/hpf in the proximal oesophagus (74.1% for both endpoints) compared to mid (59.3% for both) and distal third (61.5% and 50%, respectively), but all three segments were improved compared to placebo.

3.2.2.2 | Oesophageal Symptoms. Treatment with either ESO-101 or placebo led to symptomatic relief, with no significant difference between the treatment groups. Overall, 24 of 27 (88.9%) patients in the ESO-101 group and 10 of 13 (76.9%) in the placebo group experienced an improvement of dysphagia symptoms ($p = 0.3699$, not significant [ns]). Patients reported a mean reduction in the dysphagia severity from baseline to EoT of 3.2 ± 2.0 points in the ESO-101 group and of 3.0 ± 2.2 points in the placebo group (Figure 4A). In the odynophagia severity, both treatment groups showed similar improvement of a mean of 2.1 ± 2.6 for ESO-101 and 2.3 ± 2.5 for placebo (Figure 4C). The relative change in symptom scores from baseline was larger in the ESO-101 group than in the placebo group for both dysphagia (mean −61% vs. −47%) (Figure 4B) and odynophagia (mean −65% vs. −58%) (Figure 4D).

3.2.2.3 | Clinico-Histologic Remission. A higher proportion of patients in the ESO-101 group (12/27, 44%) achieved both symptomatic improvement and histological remission from baseline to EoT compared to the placebo group (0/13; 0%; $p = 0.0035$) (Figure 5).

3.2.2.4 | Endoscopic Severity. In the ESO-101 group, the median EREFS total score decreased from 7 at baseline (IQR 5.5–10.0) to 4.0 at EoT (IQR 1.0–5.0), whereas no substantial change was observed in the placebo group (median scores 6.0 [IQR 4.0–9.0] at baseline vs. 7.0 [IQR 5.0–8.0] at EoT; $p = 0.001$) (Figure 6). Endoscopic results in the proximal and distal oesophagus were in line with changes in the overall scores. Moreover, improvements were noted in both the EREFS' inflammatory and fibrostenotic subscores in the ESO-101 group (Tables S3, S4).

3.2.2.5 | Treatment Satisfaction. In both treatment groups, most patients (67%) were satisfied or very satisfied with the handling of the IMP. Difficulties in swallowing the capsule were reported in 41% of patients in the ESO-101 and 25% of patients in the placebo group, while all other patients were indifferent and found it easy to swallow or equal to swallowing liquid. Most patients were satisfied or very satisfied with the taste of the IMP (81% in the ESO-101 group and 83% in

TABLE 1 | Baseline demographic and clinical characteristics.

Patient characteristics	ESO-101, $n=28$	Placebo, $n=15$	Total, $n=43$
Sex, *n* (%)			
Male	22 (78.6)	11 (73.3)	33 (76.7)
Female	6 (21.4)	4 (26.7)	10 (23.3)
Age, years, mean ± SD	38.5 ± 11.7	45.0 ± 12.4	40.8 ± 12.2
Height, cm, mean ± SD	174.3 ± 9.0	172.5 ± 8.5	173.7 ± 8.8
Weight, kg, mean ± SD	77.33 ± 14.73	85.22 ± 17.81	80.15 ± 16.14
BMI, kg/m^2, mean ± SD	25.31 ± 3.53	28.61 ± 5.39	26.49 ± 4.51
History of allergic diseases, *n* (%)			
Allergy to animals	1 (3.6)	0	1 (2.3)
Drug hypersensitivity	0	2 (13.3)	2 (4.7)
Food allergy	1 (3.6)	2 (13.3)	3 (7.0)
Seasonal allergy	7 (25.0)	5 (33.3)	12 (27.9)
Asthma	5 (17.9)	2 (13.3)	7 (16.3)
Concomitant treatment with PPI, *n* (%)	9 (32.1)	2 (13.3)	11 (25.6)
Peak eosinophil count, mean eos/hpf ± SD median (IQR)	87.0 ± 59.6 72.3 (47–110)	84.7 ± 49.4 76.6 (33–139)	86.2 ± 55.6 76.6 (46–118)
EREFS total score (0–9), mean ± SD	7.7 ± 2.9	6.7 ± 2.5	7.3 ± 2.8
Prior oesophageal dilation	0 (0.0)	0 (0.0)	0 (0.0)
Dysphagia severity score (0–10), mean ± SD	5.6 ± 1.4	5.9 ± 1.7	5.7 ± 1.5
Odynophagia severity score (0–10), mean ± SD	3.5 ± 2.5	3.8 ± 3.4	3.6 ± 2.8

Abbreviations: BMI, body mass index; EREFS, eosinophilic esophagitis endoscopic reference score (based on Hirano et al. 2013); IQR, interquartile range (Q1—Q3); hpf, high-power field; *n*, number of patients; PPI, proton-pump inhibitors; SD, standard deviation.

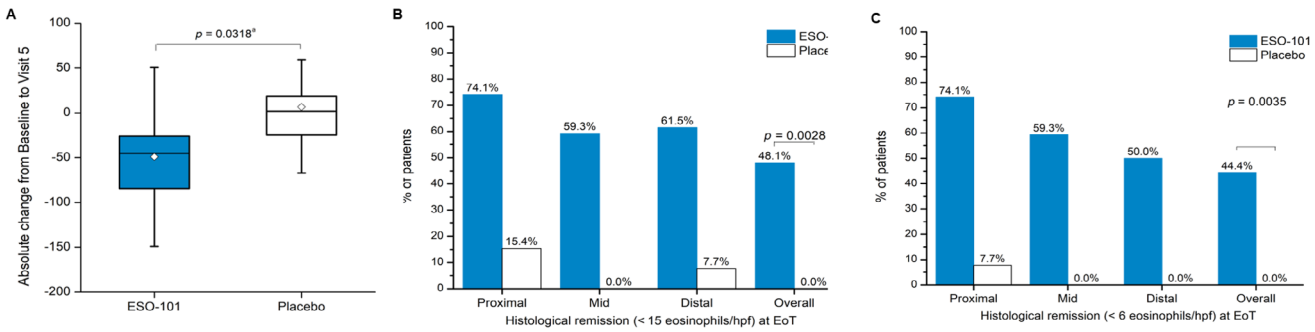

FIGURE 3 | Change in the peak eosinophil count from baseline to EoT (full analysis set). (A) Absolute change in cell count/hpf. The bottom and top edges of the box indicate the IQR (range of values between the first and third quartile). The mean value is indicated by a diamond in the box, the median value by a line. Endpoints of whiskers display the 5th and 95th percentile. [a]2-sided 2-sample *t*-test. (B and C) Proportion of patients with histological remission, defined either as (B) peak eosinophil count < 15 eosinophils/hpf or (C) peak eosinophil count < 6 eosinophils/hpf at each of the oesophageal levels. EoT, end of treatment; hpf, high-power field; IQR, interquartile range.

placebo) and the time spent on each administration of the IMP (89% in ESO-101 and 83% in placebo) (Table S5).

3.3 | Safety

Overall, ESO-101 was well tolerated, and no serious adverse events or deaths were reported. The incidence of adverse events during the treatment period was 64% and 60% in the ESO-101 and the placebo groups, respectively (Table 2), and most were rated as mild in intensity. The most frequently reported adverse events (≥ 10% of patients) were headache (14% vs. 20% in the ESO-101 and placebo arms, respectively), dyspepsia (18% vs. 0%) and dry throat (0% vs. 13%). Notably, no oral, oropharyngeal or oesophageal candidiasis was reported.

Only two patients in the ESO-101 group and four patients in the placebo group reported adverse events deemed related to the

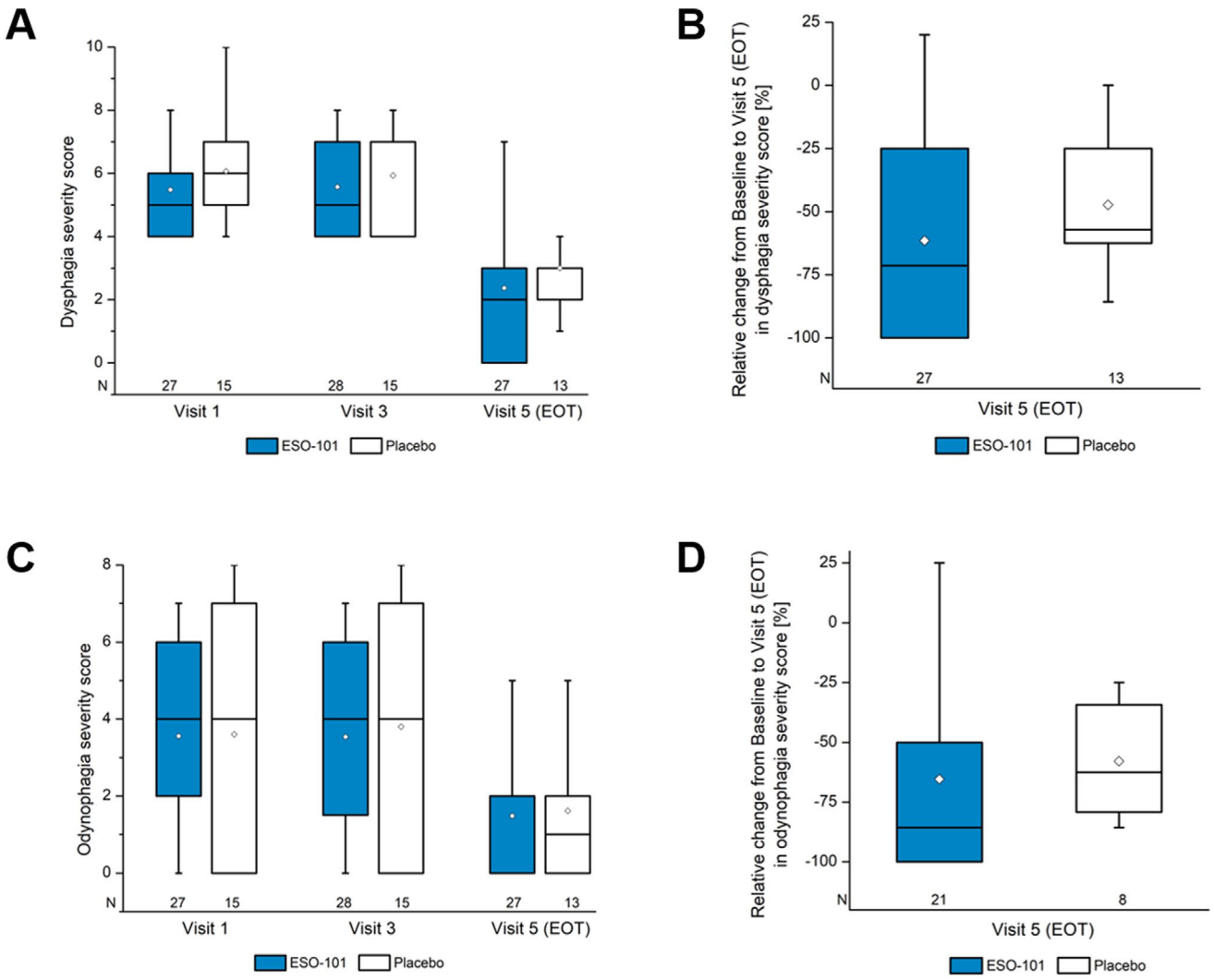

FIGURE 4 | Change in dysphagia and odynophagia symptoms from baseline to EoT (full analysis set). (A and B) Dysphagia was quantified in terms of absolute score values (A) and relative change from baseline (B). (C and D) Odynophagia was quantified in terms of absolute score values (C) and relative change from baseline (D). The bottom and top edges of the box indicate the IQR (range of values between the first and third quartile). The mean value is indicated by a diamond in the box, the median value by a line. Endpoints of whiskers display the 5th and 95th percentile. EoT, end of treatment; IQR, interquartile range; *N*, number of patients.

study medication. Among them, one patient allocated to placebo reported repeated food impaction episodes, leading to discontinuation of treatment and his/her participation in the trial. One patient in the ESO-101 group presented an adverse event related to a trial procedure, namely, dyspepsia caused by the endoscopy. One patient in the ESO-101 arm underwent hospitalisation for a planned colonic polypectomy.

In the participants receiving ESO-101 and placebo, median serum cortisol was 12.6 and 10.1 μg/dL, respectively, at baseline, and there were no significant differences between treatment groups in cortisol levels at the EoT assessment (12.1 and 12.2 μg/dL, respectively for ESO-101 and placebo). Three patients in the ESO-101 with normal serum cortisol in baseline presented a non-clinically significant reduction in EoT visit. On the other hand, one patient in the placebo group with reduced cortisol at baseline normalised it at EoT visit. The participants did not report any associated symptoms or signs of adrenal insufficiency.

4 | Discussion

Topical treatment of oesophageal diseases is challenging due to anatomical, physiological and mechanical properties of this organ, whose primary function is to quickly conduct the contents of the pharynx to the stomach. These properties limit the retention time of medications, making localised drug delivery in the oesophagus particularly difficult. This multicentre, randomised, controlled trial is the first study investigating efficacy, safety and tolerability of the EsoCap device, a novel drug delivery device to release topical medication in the oesophageal lumen. In this proof-of-concept research in adult patients with active EoE, the mucoadhesive film rolled inside this innovative drug delivery system was loaded with mometasone furoate (ESO-101 active treatment) or administered unloaded (placebo comparator). As the primary endpoint of this study, the peak eosinophil count reduced from baseline by a mean of 49.1 ± 88.4 cells/hpf in the ESO-101 group but increased by 6.6 ± 65.1 eosinophils/

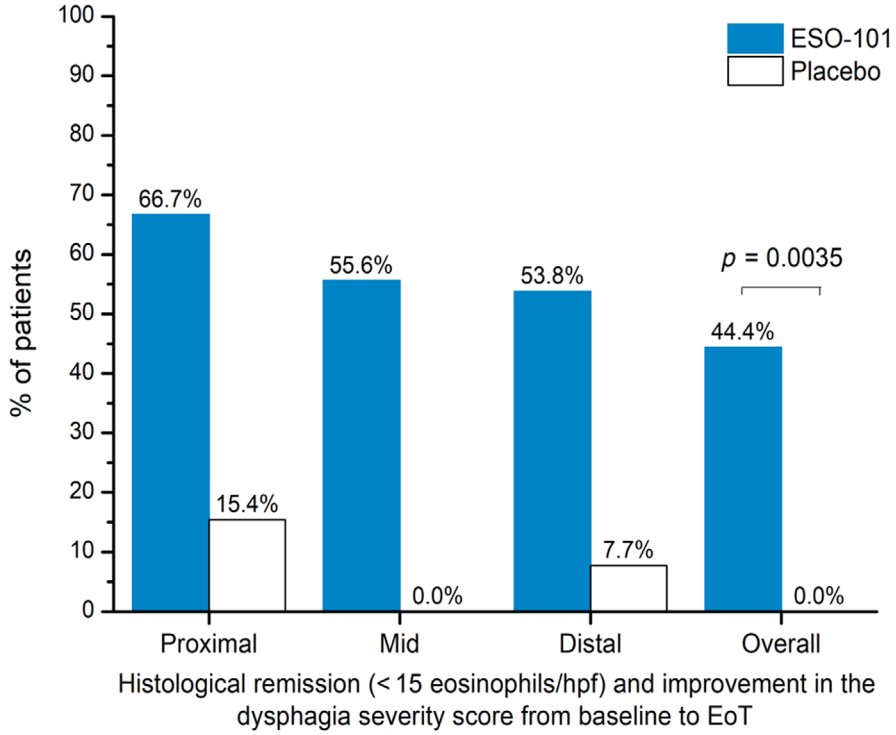

FIGURE 5 | Proportion of patients showing both amelioration of dysphagia symptoms and histological remission (< 15 eosinophils/hpf) at EoT (full analysis set).

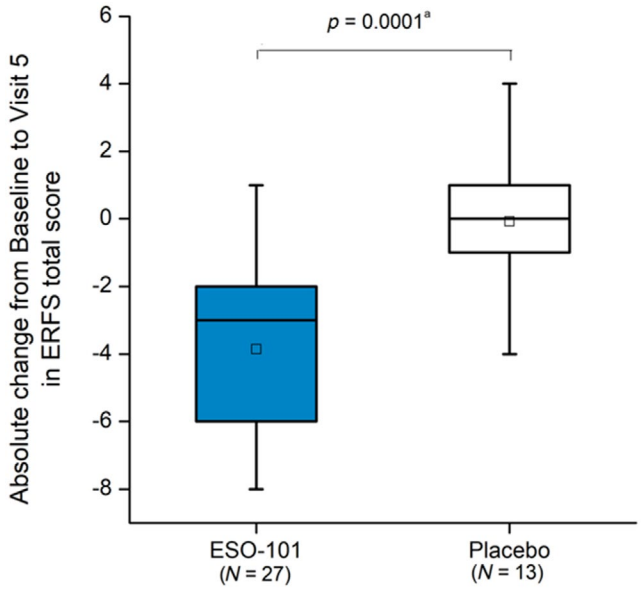

FIGURE 6 | Change in endoscopic signs of inflammation and fibrosis from baseline to EoT (full analysis set). The endoscopic response was measured based on the EREFS. The bottom and top edges of the box indicate the IQR (range of values between the first and third quartile). The mean value is indicated by a diamond in the box, the median value by a line. Endpoints of whiskers display the 5th and 95th percentile. [a]2-sided Wilcoxon rank sum test, post hoc analysis. EoT, end of treatment; EREFS, eosinophilic esophagitis endoscopic reference score; IQR, interquartile range; *N*, number of patients.

hpf in the placebo group. In addition, 48% and 44% of participants receiving ESO-101 had < 15 eosinophils/hpf and < 6 eosinophils/hpf, respectively, at EoT at all three oesophageal levels, compared with 0% in the placebo group. The total EREFS score also improved significantly among patients in the active group, and no safety issues were noted with either the active or the placebo device. However, improvement in both dysphagia and odynophagia was not significantly superior in ESO-101-treated patients when compared to placebo-treated patients.

Topical corticosteroids have been a first-line therapy for EoE since the first descriptions of the disease [24] and are the most studied therapeutic alternative in patients with EoE in clinical trials. However, for a long time, their efficacy has been only modest [5], and similar to that of other alternatives such as dietary therapy [3] or PPIs [25], especially because formulations not suitable for targeting the oesophageal mucosa were used, including inhaler formulation of fluticasone propionate or budesonide designed for asthma [10, 26–28], and oral slurries that mixed the active ingredient with different viscous vehicles [29], likely inefficient to achieve proper adherence to the oesophageal mucosa [30]. The recent development of new corticosteroid formulations, based mainly on orodispersible tablets of budesonide [31] or fluticasone [32], have contributed to improving the effectiveness in clinical and histological remission, although with a certain risk of developing oesophageal candidiasis [33].

Our study used mometasone furoate, a highly lipophilic glucocorticoid with a long half-life with extensive hepatic metabolism and no major metabolites detectable in plasma, whose efficacy and safety have been extensively documented in bronchial asthma [34], allergic rhinitis [35] and different dermatoses [36]. Systemic bioavailability of mometasone is only 0.1%, 10 times lower than that of fluticasone (~1% bioavailability) and 340 times lower than that of budesonide (34% bioavailability) [37]. Its use in EoE is limited, however, to two small observational

TABLE 2 | Treatment-emergent adverse events.

System organ class preferred term	ESO-101, $n=27$		Placebo, $n=12$		Total, $n=39$	
	n_{AEs}	n (%)	n_{AEs}	n (%)	n_{AEs}	n (%)
Any event	61	18 (64.3)	31	9 (60.0)	92	27 (62.8)
Gastrointestinal disorders	30	11 (39.3)	10	6 (40.0)	40	17 (39.5)
Abdominal discomfort	1	1 (3.6)	0	0 (0.0)	1	1 (2.3)
Abdominal pain upper	3	2 (7.1)	1	1 (6.7)	4	3 (7.0)
Diarrhoea	1	1 (3.6)	0	0 (0.0)	1	1 (2.3)
Dyspepsia	14	5 (17.9)	0	0 (0.0)	14	5 (11.6)
Dysphagia	1	1 (3.6)	0	0 (0.0)	1	1 (2.3)
Recrudescence of Eosinophilic oesophagitis	0	0 (0.0)	1	1 (6.7)	1	1 (2.3)
Erosive oesophagitis	1	1 (3.6)	0	0 (0.0)	1	1 (2.3)
Flatulence	0	0 (0.0)	1	1 (6.7)	1	1 (2.3)
Gastro-oesophageal reflux disease	1	1 (3.6)	0	0 (0.0)	1	1 (2.3)
High stomach acid symptoms	0	0 (0.0)	2	1 (6.7)	2	1 (2.3)
Large intestine polyp	1	1 (3.6)	0	0 (0.0)	1	1 (2.3)
Nausea	2	1 (3.6)	1	1 (6.7)	3	2 (4.7)
Odynophagia	2	2 (7.1)	1	1 (6.7)	3	3 (7.0)
Oesophageal food impaction	0	0 (0.0)	3	2 (13.3)	3	2 (4.7)
Oesophageal pain	1	1 (3.6)	0	0 (0.0)	1	1 (2.3)
Vomiting	2	1 (3.6)	0	0 (0.0)	2	1 (2.3)
General disorders and administration site conditions	0	0 (0.0)	1	1 (6.7)	1	1 (2.3)
Swelling face	0	0 (0.0)	1	1 (6.7)	1	1 (2.3)
Hepatobiliary disorders	1	1 (3.6)	0	0 (0.0)	1	1 (2.3)
Hypertransaminasaemia	1	1 (3.6)	0	0 (0.0)	1	1 (2.3)
Infections and infestations	3	3 (10.7)	2	2 (13.3)	5	5 (11.6)
COVID-19	0	0 (0.0)	1	1 (6.7)	1	1 (2.3)
Influenza	1	1 (3.6)	0	0 (0.0)	1	1 (2.3)
Nasopharyngitis	0	0 (0.0)	1	1 (6.7)	1	1 (2.3)
Oesophageal candidiasis	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Oral candidiasis	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Oropharyngeal candidiasis	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Pharyngitis	1	1 (3.6)	0	0 (0.0)	1	1 (2.3)
Pharyngitis streptococcal	1	1 (3.6)	0	0 (0.0)	1	1 (2.3)
Injury, poisoning and procedural complications	1	1 (3.6)	0	0 (0.0)	1	1 (2.3)
Vaccination complication	1	1 (3.6)	0	0 (0.0)	1	1 (2.3)
Musculoskeletal and connective tissue disorders	1	1 (3.6)	2	2 (13.3)	3	3 (7.0)
Back pain	1	1 (3.6)	1	1 (6.7)	2	2 (4.7)
Pain in extremity	0	0 (0.0)	1	1 (6.7)	1	1 (2.3)

(Continues)

TABLE 2 | (Continued)

System organ class preferred term	ESO-101, $n=27$		Placebo, $n=12$		Total, $n=39$	
	n_{AEs}	n (%)	n_{AEs}	n (%)	n_{AEs}	n (%)
Nervous system disorders	16	4 (14.3)	9	4 (26.7)	25	8 (18.6)
Dizziness	0	0 (0.0)	2	1 (6.7)	2	1 (2.3)
Headache	16	4 (14.3)	6	3 (20.0)	22	7 (16.3)
Somnolence	0	0 (0.0)	1	1 (6.7)	1	1 (2.3)
Psychiatric disorders	1	1 (3.6)	0	0 (0.0)	1	1 (2.3)
Initial insomnia	1	1 (3.6)	0	0 (0.0)	1	1 (2.3)
Respiratory, thoracic and mediastinal disorders	8	6 (21.4)	6	3 (20.0)	14	9 (20.9)
Cough	2	1 (3.6)	0	0 (0.0)	2	1 (2.3)
Dry throat	0	0 (0.0)	2	2 (13.3)	2	2 (4.7)
Nasal congestion	1	1 (3.6)	0	0 (0.0)	1	1 (2.3)
Oropharyngeal pain	2	2 (7.1)	0	0 (0.0)	2	2 (4.7)
Rhinorrhoea	2	1 (3.6)	0	0 (0.0)	2	1 (2.3)
Throat irritation	1	1 (3.6)	4	1 (6.7)	5	2 (4.7)
Vascular disorders	0	0 (0.0)	1	1 (6.7)	1	1 (2.3)
Hypertension	0	0 (0.0)	1	1 (6.7)	1	1 (2.3)

studies [13, 14] and a single randomised study, in which patients received 0.8 mg of mometasone furoate spray or placebo on the tongue and then swallowed [15]. Symptoms reduced significantly under active medication. However, no endoscopic or histologic assessment was performed.

Despite being secondary endpoints, some of these results warrant further discussion. First, our 4-week study is one of the shortest clinical trials carried out so far with a topical corticosteroid in patients with EoE. We hypothesize that a longer study duration could have increased the efficacy of ESO-101 in achieving histological remission, as could the use of higher doses of mometasone furoate. Second, both patient groups treated with active medication and placebo showed improved dysphagia from baseline, with only a non-significant trend towards greater benefit observed in the active medication group; the sample size was not powered to demonstrate superiority in symptomatic remission, and the short duration of the trial limited our ability to rule out a placebo effect. Additionally, using non-validated symptom scales may have hindered the ability to detect differences between the groups. Similar findings have been obtained in other very short-term trials [38]. Possible treatment-induced changes in oesophageal remodelling could not be assessed in this proof-of-concept study, since histopathological analyses did not go beyond the maximum eosinophil count per field, and other markers included in the EoE histological scoring system were not evaluated in biopsies obtained. Third, endoscopic improvement was mainly due to reductions in the EREFS inflammatory subscore. The exclusion of patients with significant oesophageal strictures and, again, the short duration of treatment prevented changes in the EREFS fibrotic subscore. Fourthly, ESO-101 was highly safe, with no serious adverse events, adrenal suppression and especially oropharyngeal or oesophageal candidiasis reported. Because of its highly lipophilic nature, mometasone deposits to a great extent in the targeted mucosa, where it binds to corticosteroid receptors with higher affinity [39], and consequently, less unbound drug is available to interact with systemic glucocorticoid receptors, reducing the potential for adverse effects. Finally, most patients were satisfied with the handling of the EsoCap device, and although some of them considered it difficult to swallow, compliance was as high as 100% in ESO-101 and 93% in the placebo group. Difficulties in swallowing mainly consisted of mild to moderate foreign body sensations while swallowing the capsule, without pain or gagging. This may well be related to hypervigilance or swallowing anxiety [40], which has been well described in EoE and other chronic oesophageal diseases even after effective treatment [41].

Our study has several strengths, including the rigorous study design and methodology, which involved patients recruited at 14 sites in 5 European countries, who exhibited clinical characteristics of adult EoE population with strengthened inclusion criteria, as it required active eosinophilic inflammation in at least two-thirds of the oesophagus. However, some limitations should be also acknowledged, including the small sample size, which was not powered to detect improvements of symptoms or other secondary outcomes, the short-term treatment phase and the single dose of mometasone tested. Furthermore, the histological and clinical remission results of ESO-101 were inferior to those reported for other formulations already marketed for the treatment of eosinophilic esophagitis. Differences in the concept behind the different therapeutic approaches and in the development status of the different options preclude direct comparisons, which should be addressed by future studies with the EsoCap technology.

In conclusion, ESO-101, a novel technology designed to adhere medication to the oesophageal mucosa, was safe and well tolerated in adults with EoE. Efficacy outcomes demonstrated improvement in both histologic and endoscopic findings and support further development of EsoCap as a unique technology for targeted and long-lasting drug delivery directly to the oesophageal mucosa with potential use in different oesophageal diseases.

Author Contributions

Alfredo J. Lucendo: conceptualization, investigation, writing – original draft. **Óscar Nantes-Castillejo:** investigation, writing – review and editing. **Alex Straumann:** investigation, writing – review and editing. **Luc Biedermann:** investigation, writing – review and editing. **Albert J. Bredenoord:** investigation, writing – review and editing. **Danila Guagnozzi:** investigation, writing – review and editing. **Leonardo Blas-Jhon:** investigation, writing – review and editing. **Anna Wiechowska-Kozlowska:** investigation, writing – review and editing. **Simon Weidlich:** investigation, writing – review and editing. **Ulrike von Arnim:** investigation, writing – review and editing. **Cecilio Santander Vaquero:** investigation, writing – review and editing. **Antonia Perelló:** investigation, writing – review and editing. **Isabel Pérez-Martínez:** investigation, writing – review and editing. **Jesús Barrio:** investigation, writing – review and editing. **Michael Vieth:** investigation, writing – review and editing. **Ghazaleh Gouya:** writing – original draft, project administration, formal analysis, data curation, conceptualization. **Evan S. Dellon:** investigation, conceptualization, writing – original draft.

Conflicts of Interest

A.J.L. receives research funding from Adare/Ellodi, AstraZeneca, Dr. Falk Pharma, EsoCap, and Regeneron and serves as a consultant for Alfasigma, Arena/Pfizer, EsoCap, Dr. Falk Pharma, EsoCap, and Sanofi. O.N.C. received funding for scientific activities from Abbvie, Falk, Takeda, Adacyte, Shire, Faes-Farma, AstraZeneca, Pfizer, Janssen. A.S. has consultant contracts Astra-Seneca, BMS-Receptos, Calypso, EsoCap, Falk Pharma, GSK, Pfizer, Sanofi-Regeneron. L.B.: Advisory for Abbvie, Amgen, BMS, Falk, Janssen, Pfizer, Lilly, Takeda, Sanofi, Esocap; Speaker for Takeda, Sanofi, Abbvie, Lilly, Dr. Falk Pharma, BMS, and Pfizer. A.J.B. received research funding from BMS, Sanofi/Regeneron, SST, MMS, and Dr. Falk Pharma and received speaker and/or consulting fees from Uniquity, Laborie, Medtronic, BMS, Dr. Falk Pharma, Calypso Biotech, Eupraxia, Aqilion, Alimentiv, Sanofi/Regeneron, Uniquity, Reckitt, AlfaSigma and AstraZeneca. D.G. receives funding for scientific activities from Tillots Pharma, Falk, Takeda, Sanofi Biotechnology, Dr. Falk Pharma, Laboratorio Salvat. S.W. received speaker and/or consulting fees from Janssen, Sanofi, AstraZeneca, MSD, Tillotts, Gilead, Abbvie, Johnson&Johnson, Takeda, Dr. Falk Pharma, and BMS. U.v.A. received speaker and/ or consulting fess from BMS, Dr. Falk Pharma, Sanofi/ Regerenon, Alfasigma, Pfizer, Lilly, Abbive, Takeda, Esocap, Johnson&Johnson, Astra Zeneca. J.B. served as a speaker, as a consultant or received research or education funding from Abbvie, Takeda, Janssen, Kern Pharma and Ferring. M.V. received honoraria as speaker from Dr. Falk Pharma and Esocap. E.S.D. receives research funding from Adare/Ellodi, Allakos, Arena/Pfizer, AstraZeneca, Celldex, Eupraxia, Ferring, GSK, Meritage, Miraca, Nutricia, Celgene/Receptos/BMS, Regeneron, Revolo, Sanofi, and Shire/Takeda. He is a consultant for Abbvie, Adare/Ellodi, Akesobio, Alfasigma, ALK, Allakos, Amgen, Apollo, Aqilion, Arena/Pfizer, Aslan, AstraZeneca, Avir, Biocryst, Bryn, Calypso, Celgene/Receptos/BMS, Celldex, EsoCap, Eupraxia, Dr. Falk Pharma, Ferring, GI Reviewers, GSK, Holoclara, Invea, Knightpoint, LucidDx, Morphic, Nexstone Immunology/Uniquity, Nutricia, Parexel/Calyx, Phathom, Regeneron, Revolo, Robarts/Alimentiv, Sanofi, Shire/Takeda, Target RWE, Upstream Bio. Educational grant provided by Allakos, Aqilion, Holoclara, Invea. The remaining authors have nothing to disclose.

Data Availability Statement

The data that support the findings of this study are available from EsoCap AG. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the author(s) with the permission of EsoCap AG.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.