


Inhaled ciclesonide is efficacious and well tolerated in the treatment of severe equine asthma in a large prospective European clinical trial

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Abstract

Background: Ciclesonide is a glucocorticoid prodrug, already registered for human use. Due to its mode of action and inhaled route of administration, it was considered an appropriate treatment option for horses with severe equine asthma. Although the efficacy of inhaled ciclesonide has been demonstrated in horses with asthma exacerbations under controlled mouldy hay challenge conditions, it has not yet been reported under field conditions.

Objectives: To assess the effectiveness and safety of inhaled ciclesonide for the treatment of severe equine asthma.

Study design: Prospective, multicentre, placebo-controlled, randomised, double-blinded study.

Methods: Two-hundred and twenty-four client-owned horses with severe equine asthma were randomised (1:1 ratio) to receive either ciclesonide inhalation (343 µg/actuation) solution or placebo (0 µg/actuation). Treatments (placebo or ciclesonide) were administered with a nonpressurised Soft Mist™ inhaler specifically developed for horses (Aservo® EquiHaler®) at doses of 8 actuations twice daily for the first 5 days and 12 actuations once daily for the following 5 days. Primary outcome was a success/failure analysis with the a priori definition of treatment success as a 30% or greater reduction in weighted clinical score (WCS) between Day 0 and Day 10 (±1).

Results: The treatment success rate (as defined above) in ciclesonide-treated horses was 73.4% (80/109) after 10 (±1) days of treatment, being significantly higher than in the placebo group with 43.2% (48/111; $P < 0.0001$). Few systemic and local adverse events of ciclesonide were observed.

Main limitations: The severity of clinical signs of severe equine asthma varies over time; despite the prohibition of environmental management changes during the study, a placebo effect was also identified. This potentially contributed, in part, to the clinical improvement observed in the ciclesonide-treated group.

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Conclusions: Ciclesonide inhalation solution administered by the Aservo[®] EquiHaler[®] effectively reduced severity of clinical signs in a majority of horses with severe equine asthma and was well tolerated.

KEYWORDS

horse, equine asthma, heaves, cough, ciclesonide, clinical trial, inhaled corticosteroids

1 | INTRODUCTION

Equine asthma is a term used to describe an environmentally induced, nonseptic inflammatory disorder of the lower airways of horses and incorporates the diseases previously known as recurrent airway obstruction (RAO), summer pasture RAO (SPRAO) and inflammatory airway disease (IAD).^{1,2} Although accepted as a heterogeneous disease with variations in genetic susceptibility and/or immunological pathways,³ all cases of equine asthma share two common characteristic features; namely, the contribution of airborne environmental exposures to disease induction and the pivotal role of inflammation in disease pathogenesis.^{3,4} Whereas strict environmental control per se can lead to improvement of clinical signs, the consistent and sustained benefits of corticosteroid therapy in all forms of equine asthma⁵⁻¹² largely reflect the universal importance of inflammation in underpinning the variety of asthma-related clinical signs, including cough, nasal discharge, increased respiratory rate, abnormal thoracic auscultatory findings, nasal flaring and increased expiratory effort at rest.^{13,14}

Although corticosteroids can be administered via the enteral, intravenous or intramuscular route, inhaled therapy is equally beneficial¹⁵ and offers the advantage of depositing the drug directly at the intended site of action, resulting in significantly lower systemic drug concentration and lowering the potential for systemic side effects.¹⁶ Currently, adoption of the inhaled route for corticosteroid administration to horses necessitates the “off-label” use of either inhaled formulations licensed for humans (eg MDIs) or the nebulisation of corticosteroid preparations (eg dexamethasone) licensed for administration to horses via other (noninhaled) routes.^{15,17} Unsurprisingly, inherent differences exist between the various methods currently adopted to deliver inhaled corticosteroids to horses, including aerosol particle size distribution, efficiency and consistency of drug deposition within the lower airways and ease of use.^{16,18} Despite the cited benefits of inhaled corticosteroid administration in equine asthma, application of these “off-label” treatment practices in horses still results in suppression of the hypothalamo-pituitary-adrenal axis (HPA) and a treatment-associated reduction in blood cortisol levels, reflecting a level of systemic absorption of active drug from the site of deposition.^{12,19-22} Ciclesonide, a glucocorticoid licensed for the treatment of allergic rhinitis and chronic asthma in humans,²³ is a prodrug which is de-esterified in the lung to the active metabolite desisobutyl-ciclesonide (des-CIC). With a 100- to 120-fold higher glucocorticoid receptor binding affinity than ciclesonide, and 12 times higher than dexamethasone,^{24,25} des-CIC is the effective drug which elicits typical glucocorticoid effects at the site of activation

in the airways, thus significantly reducing the potential for systemic adverse effects, including HPA axis suppression.

Current evidence supporting the clinical efficacy of corticosteroid inhalation in equine asthma is largely based on the direct measurement of lung function and airway inflammation in relatively small cohorts of horses, with limited information on the meaningful clinically detectable impact of this therapeutic approach.¹⁵ To date, no large-scale clinical field trials have been conducted to assess the benefits of inhaled corticosteroid therapy in equine asthma.

We hypothesised that the combination of inhaled ciclesonide with a novel inhalation technology (Aservo[®] EquiHaler[®]) would improve the clinical signs of severe equine asthma compared with placebo and would have a good safety profile. The novel inhalation technology comprised a nonpressurised soft mist drug delivery method, specifically designed for horses.

2 | MATERIALS AND METHODS

2.1 | Study design

The trial was conducted as a multicentre prospective, randomised, double-blinded, placebo-controlled clinical study with parallel group design according to Good Clinical Practice (GCP) guidelines with client-owned horses in 24 study sites (equine practices) in Germany, Switzerland and France. Each study site had one study investigator (primary veterinarian) and not more than one co-investigator. Study investigators were qualified equine practitioners and were responsible for the recruitment of study animals and proper conduct of the study. Data were collected between November 2015 and November 2016. Study investigators, owners and data analysts were blinded to the treatment regimen of the horses.

Horses were examined before (Day 0) and at the end of treatment (Day 10 ± 1) by the study investigators. Physical examination, effectiveness assessment and blood sample collection were performed during the visits. Additionally, the owners of included horses were requested to describe their horse's quality of life (QOL) on Day 0, Day 10 (± 1) and also by telephone on Day 5 (± 1).

2.2 | Animals and inclusion/exclusion criteria

Client-owned, adult horses of any sex and breed, housed in their usual environment and routinely diagnosed with severe equine

asthma by the study investigators, were eligible for inclusion if provided owner informed consent (OIC) was obtained and the horses complied with all predetermined inclusion and exclusion criteria assessed via a standardised screening procedure. By signing the OIC, owners agreed to inclusion and participation of their horse in the study and consented to telephone contact being made by the attending study investigator during the study.

Horses were eligible for study inclusion if they fulfilled all of the following criteria: (a) moderate to severe clinical signs of equine asthma, as defined by a weighted clinical score (WCS) ≥ 11 , adapted by Tesarowski et al²⁶; (b) laboured breathing at rest and the presence of an exaggerated abdominal component to expiration ("abdominal lift score ≥ 1 "); (c) a greater than 14 day duration of the current clinical episode, as defined by the presence of at least one disease-associated clinical sign (eg nasal discharge); (d) evidence of chronicity in the animal's medical history, as defined by the occurrence of at least two clinical episodes of equine asthma in the past and (e) prior evidence of a clinical improvement following the administration of a bronchodilator and/or glucocorticoid and/or implementation of a change in environment.

Horses were ineligible for inclusion in the study if they fulfilled one of the following exclusion criteria: (a) a suspected systemic infectious disease, (b) known upper respiratory tract functional disorder, which interfered with respiration at rest, (c) an impetuous temperament which might have precluded appropriate use of the EquiHaler[®], (d) pretreatment with triamcinolone within 8 weeks, systemic pretreatment with long acting or depot glucocorticoid (eg betamethasone, dexamethasone-depot) within 6 weeks and systemic pretreatment with short-term glucocorticoids or inhaled glucocorticoids, bronchodilators, systemic antibiotics or other respiratory therapy (eg secretolytics, expectorants, mucolytic agents) within 2 weeks prior to inclusion (e) change in environment or feeding within 2 weeks prior to inclusion in the study, (f) any comorbidity/condition or suspected or confirmed concomitant disease that was likely to preclude study completion or interfere with study results and (g) pregnant or lactating.

The administration of routine treatments (eg vaccinations, antiparasitic drugs) considered not to have an impact on the clinical condition investigated (ie exacerbated environmental respiratory disease) was permitted. Throughout the duration of the study, animals were kept in their usual environment and their management, exercise and dietary regimes remained the same.

2.3 | Treatment

Horses were randomly assigned, at a ratio of 1:1, to receive either inhaled ciclesonide solution or an inhaled placebo solution. The randomisation scheme, using the program PMX CTM Release 3.3.0 HP2, Propack Data GmbH, Germany, defined three-digit case numbers in a consecutive manner and a block length of 4. Each investigator was provided with a defined number of cases on the randomisation scheme such that an equal number of ciclesonide and placebo-treated horses could be included at each study site, thus minimising any site-associated treatment bias.

Inhaled treatment was administered by the owner using a newly developed inhaler based on Respimat[®] technology (called "EquiHaler[®]"), consisting of a nostril adapter attached to a soft mist inhaler (SMI) core unit. During breathing, deflection of a respiration indicator ("breath indicator") located in the chamber wall of the nostril adapter facilitated easy identification of inspiration and expiration. Placebo was administered using the EquiHaler[®] with cartridges containing the excipients (ethanol, purified water) but lacking ciclesonide. Owners were instructed in detail by the study investigator on how to use and clean the EquiHaler[®] prior to first use.

For the first 5 days of the study period, horses were administered 8 actuations of either ciclesonide (1 actuation delivers 343 μg ciclesonide) or placebo solution twice daily, approximately 12 hours apart. For the subsequent 5 days of the study, horses were administered 12 actuations once daily, either in the morning or the evening. This selected dosing regimen was based on data derived from prior dose titration studies aimed at identifying appropriate dose administration frequencies, conducted on environmentally challenged asthma-susceptible research horses.²⁷

2.4 | Assessments

The clinical condition of severe equine asthma was assessed using a WCS (Table S1), adapted from a previously described scoring system^{26,27}; to mitigate subjective variations in the application of the scoring system, all study investigators received live training on the use of the WCS, both in horses with and without respiratory signs. Additional training material included an audio presentation representing lung sounds and a video representing other clinical variables (eg breathing strategies/effort) included in the WCS. The same investigator assessed the WCS for each horse at both study visits in all cases. All horses underwent a physical examination and were assigned a WCS prior to commencement (Day 0), and following completion (Day 10 ± 1), of the study. Horses with a score ≥ 15 were classified as severely affected, those with a score between 11 and 14 as moderately affected and horses with a score between 5 and 10 as mildly affected as per previous study which correlated WCS in relation to pulmonary resistance in severely asthmatic horses.²⁷ The bodyweight of horses was estimated based on girth circumference and body length.²⁸ At the time of the physical examinations, venous blood samples were collected into EDTA and plain tubes for subsequent analysis (Vet Med Labor GmbH, Ludwigsburg, Germany). At commencement (Day 0), on Day 5 (± 1) and following completion (Day 10 ± 1) of the study, owners were requested to assess their horse's quality of life based on attitude, energy level, human interactions and general behaviour. Temporal changes from Day 0 were recorded on a three-tier ordinal scale; namely, "improved", "same" or "worsened". Safety assessment was based on reported adverse events and blood parameters.

2.5 | Data analysis

Sample size determination was performed a priori based on available data from a previous clinical field study (data not published).

In this study, 17 of 24 (approx. 70.8%) of ciclesonide-treated horses and 5 of 15 (approx. 33.3%) of placebo-treated horses showed at least a 30% reduction in WCS between Day 0 and Day 10 (± 1). Since these rates were estimated based on low sample size, a safety margin was incorporated and improvement rates were conservatively estimated as 16 of 24 (approx. 66.7%) in the ciclesonide group and 6 of 15 (approx. 40.0%) in the placebo group. A power of 95% was selected to additionally reflect remaining uncertainty about assumed success rates based on low numbers of horses in the previous field study. A two-sided Chi-square test with alpha 0.05 required 176 horses to detect a difference in treatment responder rates ($\geq 30\%$ reduction in clinical score) between treatment groups. A drop-out rate of 20% of horses was expected and in order to compensate for this loss of information, $220 = \frac{176}{0.8}$ horses were randomised.

Statistical analyses were conducted using the SAS[®] System Version 9.4. Different populations were defined for analysis. The safety set (SAF) encompassed all enrolled animals who received at least one dose of study medication and was used for safety assessment. Primary efficacy analysis was performed on the full analysis set (FAS) comprising all SAF members complying with all inclusion and exclusion criteria, following the Intention to Treat principle. The *per protocol* set (PPS) was used for robustness analysis and represented a subset of FAS following removal of all cases with important protocol violations.

To avoid loss of evaluable study data, missing scoring data were addressed by applying the “last observation carried forward” (LOCF) technique, whereby missing scores were imputed by available information from unscheduled visits performed prior to study exclusion.

The primary analysis result of this study was confirmed by an appropriate sensitivity analysis that excluded all animals with incomplete scoring data. The leading variable for the efficacy assessment was the treatment response rate, whereby a “treatment responder” was defined as an animal with a WCS reduction in at least 30% between Day 0 and Day 10 (± 1). The null hypothesis (*viz.* rate of responders = rate of nonresponders) was tested by means of a two-sided Chi-square test with error probability $\alpha = 0.05$. A quantifiable measure of the treatment advantage was provided by calculation of the risk difference, including 95% confidence interval.

Further analysis was also applied to various secondary variables; these included the mean change in WCS over the treatment period, individual components of the WCS and the owners QOL assessments. Statistical test procedures (t-test, χ^2 -test) were employed to further substantiate the results.

3 | RESULTS

3.1 | Demographics

A total of 224 horses were enrolled (Figure 1), with 223 horses included in the safety analysis (SAF) and 220 included in the primary efficacy analysis (FAS). Ciclesonide and placebo-treated groups were balanced for age, bodyweight, gender, breed, disease history and vital parameters (heart rate and body temperature) at the point

of inclusion (Table S2). In the overall study population, males were over-represented. At the time of inclusion, the mean WCS of horses in the ciclesonide and placebo-treated groups were 15.3 ± 2.8 and 14.9 ± 2.6 respectively.

Seven horses in the ciclesonide-treated group and 10 horses in the placebo-treated group received concomitant, but not prohibited, treatment. The dopaminergic agent pergolide mesylate was the most commonly reported concomitant treatment administered (4 animals in the ciclesonide and 4 animals in the placebo group), consistent with Pituitary Pars Intermedia Dysfunction being the most frequently reported comorbidity at enrolment (4 horses in the ciclesonide group and 5 horses in the placebo group).

3.2 | Effectiveness

For the ciclesonide group, the primary analysis revealed a treatment responder rate of 73.4% (80/109), compared to 43.2% (48/111) for the placebo group (Table 1). This equated to a positive and significant ($P < 0.0001$) risk difference of 30.2% points (CI 95% 17.8-42.6).

Statistical analyses of the secondary variables also showed significant differences in favour of the ciclesonide treatment. The mean WCS reduction after 10 days of treatment was 7.2 ± 4.8 (CI 95% 6.3-8.1) in the ciclesonide-treated group, compared to 3.8 ± 4.5 (CI 95% 2.9-4.6) in the placebo group ($P < 0.0001$) (Figure 2). Furthermore, the reduction in WCS after ciclesonide administration was greater in horses with severe clinical signs at the time of enrolment compared with horses with moderate clinical signs (Table 2). In contrast, no such difference was observed in the placebo group.

The LOCF principle was applied to 6 cases (1 ciclesonide-treated horse and 5 placebo-treated horses), which failed to reach Day 10 (± 1) for various reasons. When analysed individually, the improvement for each of the 9 WCS clinical parameters was superior for the ciclesonide-treated group (compared with the placebo-treated group), thus demonstrating that the relatively greater reduction in WCS in the ciclesonide-treated group was not solely attributable to a single clinical parameter.

Finally, owners perceived an improved Quality of Life (QOL) after 5 (± 1) and 10 (± 1) days of treatment in 60.2% (65/108) and 69.3% (75/108) of ciclesonide-treated horses, compared to 32.7% (36/110) and 43.4% (46/110) of placebo-treated horses (Figure 3). This equated to a positive and significant ($P \leq .0001$) risk difference of 27.5% (CI 95% 14.7-40.2) and 26.1% (CI 95% 13.2-38.9) after 5 (+1) and 10 (+1) days of treatment respectively.

3.3 | Safety

Inhaled drug administration with the EquiHaler[®] was well tolerated by the enrolled horses. The overall number of adverse events (AEs) was low and equally distributed between the ciclesonide- and placebo-treated groups, with 11 AEs in 5 horses in the

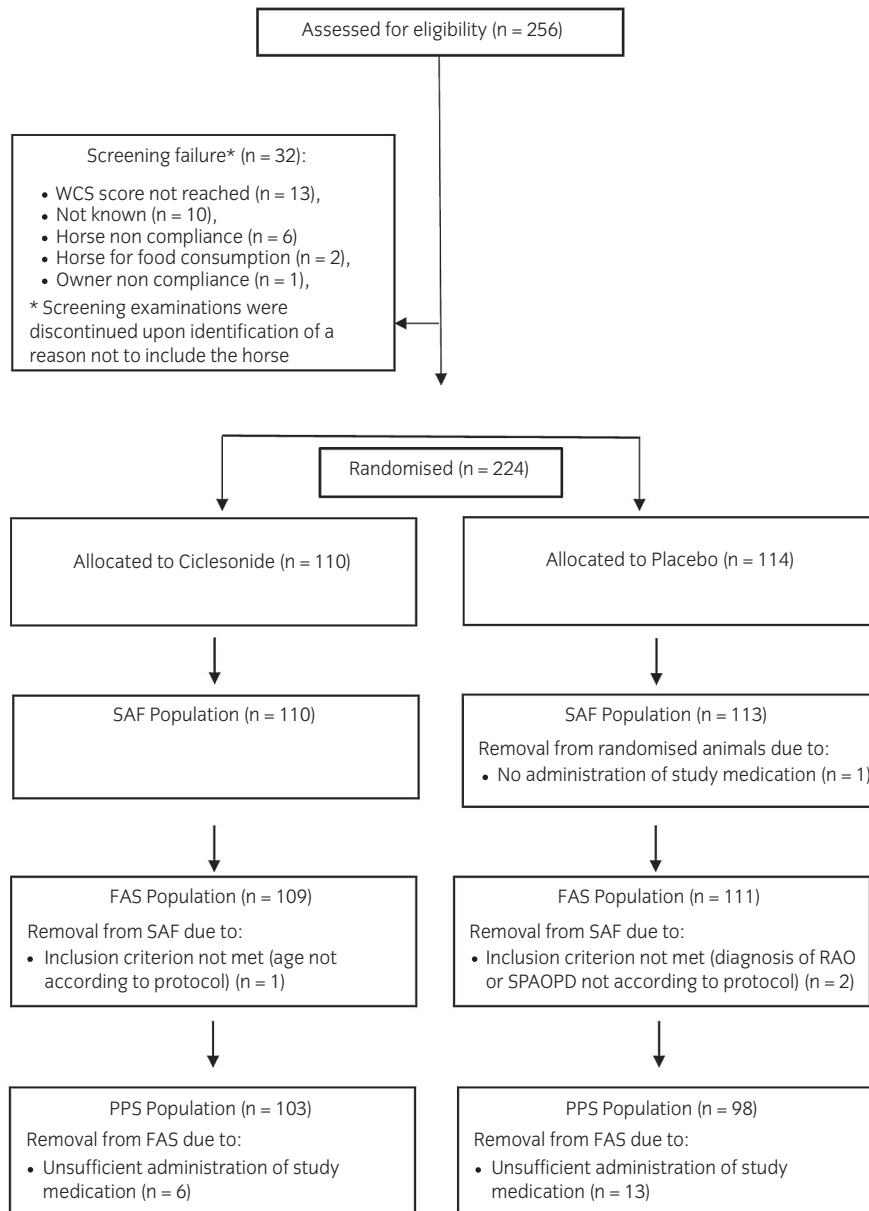


FIGURE 1 Participant flow

Parameter	Success	Ciclesonide (n = 109)	Placebo (n = 111)
		N (%)	N (%)
Treatment Success	Yes	80 (73.4%)	48 (43.2%)
	No	29 (26.6%)	63 (56.8%)
Pearson Chi-Square Test (2sided)	P-value	<.0001	
Risk Difference	Estimation	0.3015	
	95% CI	(0.1775 , 0.4255)	
Risk Ratio	Estimation	1.6972	
	95% CI	(1.3334 , 2.1603)	

Risk of Success: Risk Difference = Ciclesonide - Placebo, Risk Ratio = Ciclesonide vs Placebo

TABLE 1 Comparison of treatment response for $\geq 30\%$ reduction in weighted clinical score between ciclesonide and placebo (full analysis set population)

ciclesonide-treated group and 13 AEs in 8 horses in the placebo-treated group. No serious adverse events were reported in either group (Figure 4). Compared with mean baseline values, no clinically

relevant deviations were noted in routinely measured haematological and biochemical analytes in the ciclesonide-treated group at the conclusion of the study (Tables S3 and S4).

FIGURE 2 Change in mean Weighted Clinical Score between Day 0 and Day 10 (± 1) (FAS population)

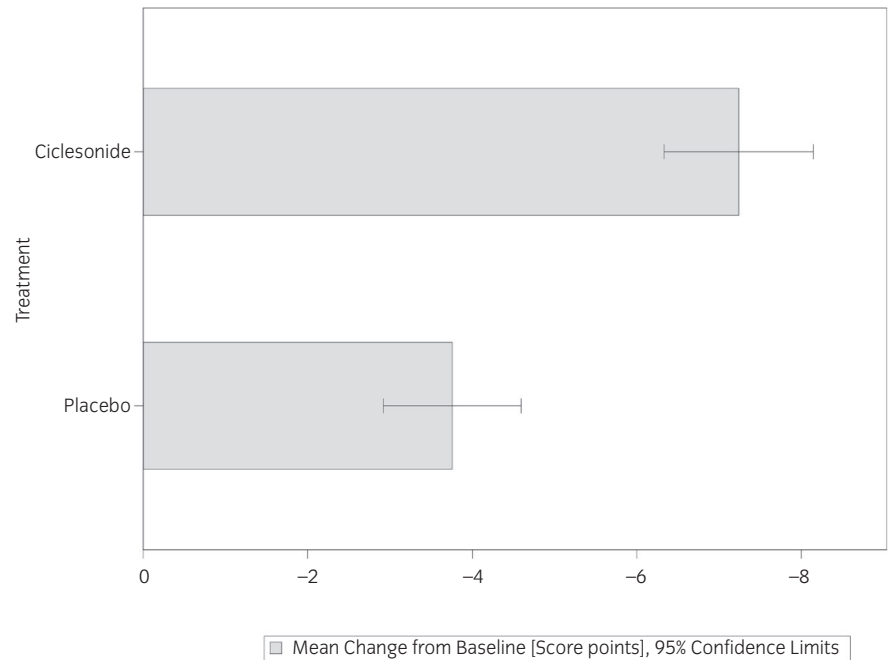


TABLE 2 Change in weighted clinical score between Day 0 and Day 10 (± 1) by severity of clinical signs at the initial visit in the ciclesonide and placebo group (full analysis set population)

Clinical signs at initial visit	Treatment	N Obs	Mean (SD)	Treatment difference		
				Mean (SE)	95% CI	P-value
Moderate	CICLESONIDE	51	-6.1 (4.17)	-2.3 (0.82)	(-3.9,-0.6)	.007
	PLACEBO	61	-3.8 (4.45)			
Severe	CICLESONIDE	58	-8.3 (5.05)	-4.6 (0.93)	(-6.4,-2.7)	<.0001
	PLACEBO	50	-3.7 (4.51)			

Method = Pooled (equal variances)

Note: N Obs, Numbers observed; 95% CI, 95% confidence interval; SD, Standard deviation; SE, Standard Error

4 | DISCUSSION

In this study, we provide high-quality evidence that inhaled ciclesonide (Aservo[®] Equihaler[®]) effectively ameliorates clinical signs of severe equine asthma in a large-scale field trial and is well tolerated. This corroborates both the reported efficacy of inhaled ciclesonide in severely asthmatic horses with experimentally induced disease exacerbation²⁷ as well as the already observed favourable safety profile.

In the absence of pulmonary function measurements, the adopted weighted clinical scoring system was applied to assess the disease status of the enrolled horses and the effectiveness of the administered drug. The scoring system, an adaptation of one established by Tesarowski et al,²⁶ was previously applied to horses with experimentally induced airway obstruction and confirmed as a good predictor of pulmonary function.²⁷ Accordingly, we used a score of ≥ 11 , together with other inclusion criterion (eg laboured breathing at rest), to provide a level of assurance that all horses at the time of enrolment had signs consistent with exacerbation

of severe equine asthma. Although airway inflammation is a hallmark feature of equine asthma, lower airway cytology is an inappropriate endpoint in the assessment of treatment effectiveness. Furthermore, in severe equine asthma, there is a poor correlation between the magnitude of airway neutrophilic influx and the severity of airway obstruction, the main determinant of clinical severity (eg increased expiratory effort)²⁹ and corticosteroid monotherapy consistently fails to result in a level of improvement in airway cytology despite the reversal of airway obstruction.^{21,30-32} Consequently, and in face of lack of portable and easily accessible pulmonary function testing modality for field use, we opted to focus on clinical signs, as this is the main outcome of interest in clinical practice.

In this study, a 30% reduction in clinical score was considered to reflect a clinically relevant improvement, an endpoint which was significantly achieved with greater frequency in ciclesonide-treated horses, compared with those receiving placebo. The adopted "responder criterion" was based on data derived from the previously published dose finding studies,²⁷ in which oral

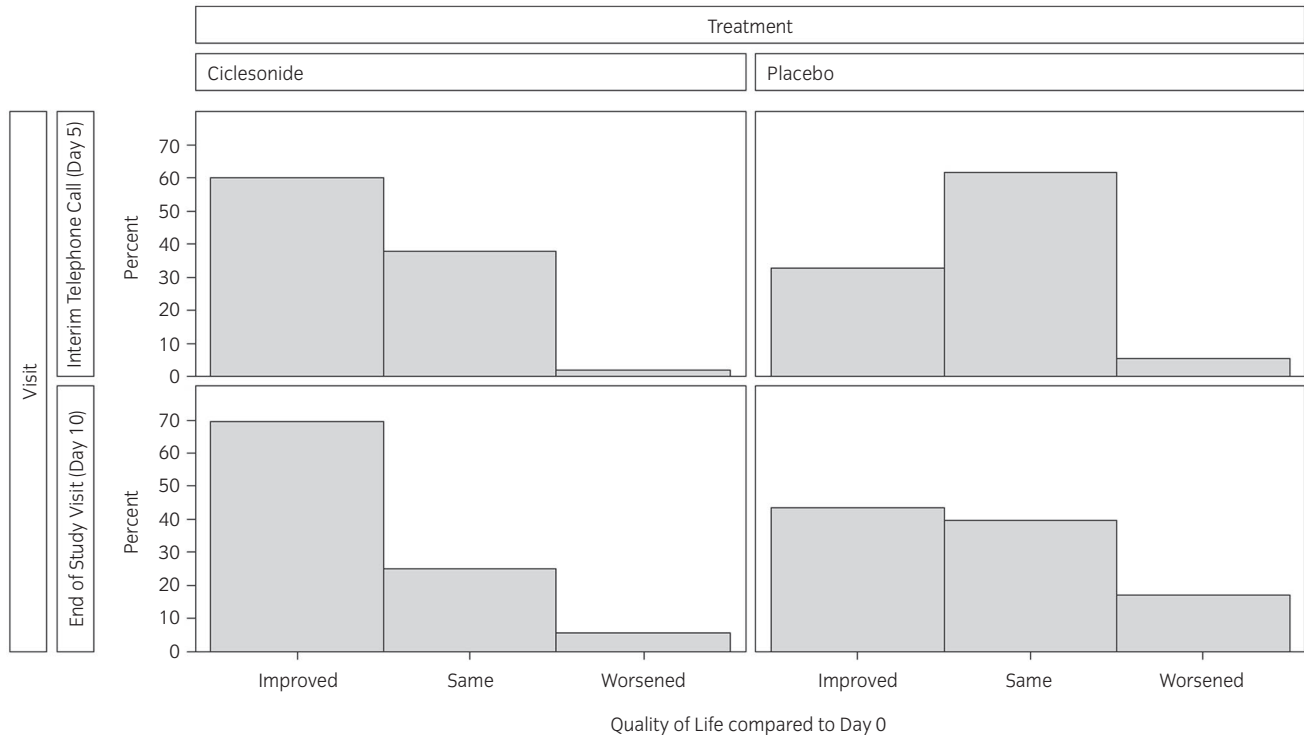


FIGURE 3 Owner assessment of change in quality of life on Day 5 (+1) and Day 10 (+1) compared with Day 0 (FAS population)

dexamethasone, regarded as “gold standard”, as well as ciclesonide, but not placebo administration, resulted in a greater than 30% improvement in both lung resistance (RL) and mean WCS, in the face of continued induced environmental challenge. This threshold was also confirmed in a pilot study, in which responder rate was 70.8% for ciclesonide, and 33.3% for placebo-treated horses (data not published). Furthermore, when disease severity was categorically graded (mild, moderate and severe) based on a linear regression curve of WCS plotted against RL,²⁷ a reduction in WCS of 30% ensured an improvement in at least one severity grade; namely, moderate to mild and severe to moderate (except horses which were included with a total score of ≥ 21). Moreover, the magnitude of change in RL underpinning the change in severity grade assessed in the dose finding studies²⁷ exceeded the lower limit of 0.63cm-H₂O/L/s (95% CI 0.33-0.94) recently reported by Calzetta et al as the minimal change in RL which can be appreciated by a meaningful improvement in clinical signs following bronchodilator treatment of severe equine asthma.³³

Importantly, the clinical relevance of the favourable response to ciclesonide administration was further substantiated by the owner's perception of change in their horse's QoL; indeed, the percentage of ciclesonide-treated horses considered to have an improved QoL largely mirrored that of ciclesonide-treated horses with a minimum 30% improvement in WCS.

To date, there are no studies investigating the inter- and intra-rater reliability of the WCS implying a potential limitation of the study. That said, all possible attempts were made to minimise inter- and intra-rater variability. This included the provision of thorough training both at a plenary meeting which included practical exercises

and the supply of instructional video and audio material. To minimise inter-rater variability, assessments on a single horse at Days 0 and 10 (+ 1) were always performed by the same investigator, and relative change was used as primary endpoint.

The increased popularity of inhalation therapy in horses can largely be attributed to the perceived reduced risk of systemic side effects due to the local delivery of drug within the airways.¹⁶ These considerations particularly apply to the administration of corticosteroids, especially as the efficacy of this approach is comparable with systemic drug administration in the treatment of equine asthma.¹⁵ Inhalation of ciclesonide showed a good safety profile in horses, as demonstrated by the absence of clinically relevant deviations in routinely measured blood values, the low number of reported adverse events in the ciclesonide-treated group and the equal distribution of adverse events between the ciclesonide- and placebo-treated groups, confirming previous data.²⁷ Low glucocorticoid receptor affinity of the pro-drug, enzymatic hydrolytic conversion of ciclesonide to the active metabolite (des-CIC) at the site of deposition (ie airways), high glucocorticoid receptor affinity of des-CIC and prolonged pulmonary retention of des-CIC via the reversible formation of fatty acid esters are all factors contributing to the high safety profile of inhaled ciclesonide.^{24,25,34,35} In contrast to other glucocorticoids,^{12,19-21} ciclesonide did not suppress serum cortisol in horses,²⁷ a finding which may also contribute to the safety profile observed in the present study.

Administration of both ciclesonide and placebo was achieved using the EquiHaler[®], a Soft Mist[™] inhaler (SMI) based on the existing Respimat[®] technology already established in human inhalation therapy.³⁶⁻³⁸ As such, this method of aerosol delivery differed from

FIGURE 4 Number of adverse events classified according to VeDDRA System Organ Classes (SAF population, NOS: Not otherwise specified)



those more commonly adopted in equine inhalation therapy; namely, via jet, ultrasonic or mesh nebulisation or the use of a pressurised metered dose inhaler (MDI).¹⁶ The aerosol delivered from a SMI has a fine particle fraction greater than a pressurised MDI and a low velocity, both of which are key factors in allowing for deep lung deposition of inhaled drugs.

The overall acceptance of the EquiHaler[®] among the studied cohort was either described as “very good” or “good”, with only six horses (2.7%) being removed after the study start due to documented horse or owner noncompliance. This was in line with the results of a previous unpublished study and is not consistent with a likely relationship between nonresponders and noncompliance.

A noteworthy challenge when assessing drug efficacy in severe equine asthma is the inevitable fluctuation in the severity of clinical signs under field conditions and the associated likelihood of identifying a placebo effect in some cases. The stipulation that horses could only be included if the duration of their current clinical episode exceeded 14 days prior to enrolment offered greater assurance that

the level of airway obstruction at the time of enrolment was more established, thus minimising the likelihood of including horses which might exhibit fluctuating and temporary expressions of disease, potentially through transient and dynamic alterations in airway calibre (eg bronchospasm). Despite this condition, an apparent improvement in some placebo-treated horses was evident over the duration of the study, which, considering the exclusion criteria adopted, could not be attributed to pre- and/or co-administration of other potentially beneficial drugs. The management systems incorporated within the study were reflective of those applied to the general equine population and were considered to be major determinants of disease exacerbation at the time of enrolment. Consequently, prohibition of any change to the system throughout the duration of study was considered more important than the type of system per se. However, despite this stipulation, there remained the potential for temporal fluctuations in natural airborne exposures, outside of control of the participating veterinarians, to result in spontaneous clinical improvements in a proportion of horses. The likelihood of such

temporal variations would have been reduced if hay was the sole antigenic source, the same batch was fed throughout the entire study and the horses were permanently housed, akin to most controlled experimental challenge models³⁹⁻⁴²; however, this was not a feasible option in such a large-scale field study. In contrast, such fluctuations may be more likely if the inciting exposures were associated with the outdoor environment (eg pasture-associated asthma [*syn* SPRAO] or supplementary hay feeding at pasture) whereby variable ambient conditions such as humidity, wind direction and wind speed are major determinants of the level of exposure.⁴³ In severe equine asthma, maximal improvements in lung function following environmental change alone generally takes several weeks,⁴⁴⁻⁴⁶ a period which can be significantly reduced by the co-administration of corticosteroids.^{5,44} That said, this sole therapeutic approach can induce significant improvements in lung function in as little as 3 days, albeit that further improvements ensue over subsequent weeks of improved environmental conditions.⁴⁶ Therefore, it is feasible that a change in the level of airborne antigen challenge throughout the 10-day duration of our study, although unlikely to induce normalisation of lung function, may have induced a clinical improvement in a proportion of horses, including those receiving placebo. The fact that the potential for such an occurrence applied equally to both groups offered greater assurance that significant intergroup difference in responder rates was attributable to the administered ciclesonide.

In conclusion, the administration of inhaled ciclesonide with the novel soft mist inhalation technology to horses with severe equine asthma proved to be both clinically efficacious and safe. The excellent safety profile of ciclesonide and the applied inhalation technology (Aservo[®] EquiHaler[®]) with the potential for improved drug delivery offer a relevant progress in equine asthma treatment.

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CONFLICT OF INTERESTS

B. Albrecht, O. Engel and M. von Salis-Soglio are employees of Boehringer Ingelheim Vetmedica GmbH, the marketing authorisation

holder of Aservo[®] EquiHaler[®] with ciclesonide as active ingredient. H.-W. Mueller is an employee of Boehringer Ingelheim Pharma GmbH & Co KG. R.S. Pirie has acted as consultant to Boehringer Ingelheim Vetmedica GmbH. B. Albrecht is co-inventor on a patent regarding the use of ciclesonide in horses.

AUTHOR CONTRIBUTIONS

M. von Salis-Soglio designed the study with support from R.S. Pirie and B. Albrecht. O. Engel was responsible for data acquisition together with B. Albrecht and M. von Salis-Soglio. H.-W. Mueller performed the statistical analysis with input from O. Engel and M. von Salis-Soglio. All authors contributed to analysis and interpretation of data pertaining to the study. R.S. Pirie and M. von Salis-Soglio wrote the manuscript, with support from all authors.

ETHICAL ANIMAL RESEARCH

Permission to complete this work was obtained from Veterinary Agency of Kanton Aarau and Office of Agriculture and Nature of Kanton Berne (Authorisation Nr: 75,681) and National Agency of Veterinary Medicine (ANSES): Authorisation Nr: ENR/KLD EL-00798-0. A number of authorities in Germany were notified (Table S5).

INFORMED CONSENT

Owners gave consent for their animals' inclusion in the study.

DATA ACCESSIBILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/evj.13419>.

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SUPPORTING INFORMATION

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

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