Veterinary Record Open

Evaluation of a single-administration ototopical treatment for canine otitis externa: a randomised trial

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/vetreco-2017-000219).

To cite: Blake J, Keil D, Kwochka K, *et al*. Evaluation of a single-administration ototopical treatment for canine otitis externa: a randomised trial. *Veterinary Record Open* 2017;**4**:e000219. doi:10.1136/vetreco-2017-000219

Received 11 January 2017
Revised 18 August 2017
Accepted 25 September 2017

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ABSTRACT

Objective To evaluate the efficacy and safety of a new, single-administration Otic Solution containing florfenicol, terbinafine and mometasone furoate for the treatment of canine otitis externa (OE).

Design The clinical efficacy and safety study was a multicentre, controlled, masked and randomised field study conducted over 30 days. Two hundred and twenty -one (221) client-owned dogs of varying breeds with diagnosed bacterial and/or fungal OE were enrolled.

Procedure Dogs were randomised to either Otic Solution or control groups. Evaluations were conducted over a minimum period of 30 days with a primary effectiveness endpoint based on the improvement in a clinical severity score at the final visit (day 30). Safety analyses were based on clinical and laboratory parameters and the occurrence of adverse events.

Results The Otic Solution group demonstrated a significantly higher treatment success rate compared with that observed for the control group (72.5 per cent v 11.1 per cent, P value=0.0001) for cases of OE caused by *Staphylococcus pseudintermedius* and *Malassezia pachydermatis.* No significant safety findings were reported.

Conclusions/clinical relevance This new ototopical formulation provides safe and effective treatment of canine OE and is an important alternative antimicrobial for this indication. The single-administration dosage regimen eliminates opportunities for client dosage administration errors and medication stockpiling.

INTRODUCTION

Canine otitis externa (OE) is a relatively common disease characterised by inflammation of the epithelial tissue of the external auditory canal. The presence of OE is easy to diagnose upon completion of a thorough history, as well as physical and otoscopic examination of the patient. Physical findings indicative of OE may include erythema, swelling, scaling, crusting, discharge, malodour and pain upon palpation of the auricular cartilage. OE is a frequent cause of visits to the veterinary clinic, and while the diagnosis may be straightforward, its aetiology may not. OE may be associated with primary causes, that is, those that create disease in a *normal* ear, and secondary causes (also referred to as perpetuating factors), which enable disease in an *abnormal* ear.[1] In addition, certain animals may be predisposed to this condition, making it more likely that secondary infections will occur.[1 2]

Common bacterial pathogens associated with the perpetuation of canine OE include *Staphylococcus spp*, *Streptococcus*, *Pseudomonas*, *Proteus* and *Escherichia coli*, with *Staphylococcus pseudintermedius* being the most frequent. The most common fungal pathogen isolated is the budding yeast *Malassezia pachydermatis*.[1 3–5] Because OE may be caused and perpetuated by multiple factors, combination ototopical products are frequently used as a first-line treatment to combat the various microorganisms as well as the inflammation generally present in dogs at the time of diagnosis.[3] Treatment of canine OE frequently involves a variety of agents with antibacterial, antifungal and anti-inflammatory properties, the choice of which is most often driven by findings on otoscopic examination as well as cytological and/or culture results from ear canal exudates.[1 6] In addition to choosing an appropriate antimicrobial agent, successful resolution of OE requires delivery of a sufficient volume of the agent directly into the ear canal to make immediate contact and allow penetration into the cells and fluid within the canal. The potential difficulty for pet owners to deliver a sufficient volume (and at a frequent enough interval) of medication into the dog's ear canal must also be considered, keeping in mind that the animal may also be experiencing discomfort and/or pain. A new combination product has been developed that allows for a single-dose administration of medication by a veterinary practitioner, removing the issue of owner and pet non-compliance with medication administration, and thus optimising the chance for a successful outcome. Another potential benefit of the dosing regimen is the avoidance of potential drug stockpiling by dog owners and subsequent use without veterinarian direction.

The purpose of this manuscript is to describe the results of studies evaluating the field clinical efficacy and safety of a prescription, combination product for canine OE. The product (Claro Otic Solution; Animal Health Division, Bayer) contains florfenicol, terbinafine hydrochloride and mometasone furoate. Each of the product's three active ingredients was chosen after careful consideration of its efficacy and safety profile. This product, herein referred to as Otic Solution, has been recently approved as a single, 1-ml application to each ear for the treatment of OE in dogs associated with susceptible strains of yeast (*M pachydermatis*) and bacteria (*S pseudintermedius*).

Florfenicol, the antibacterial component of this new product, is a broad-spectrum antibiotic and fluorinated derivative of chloramphenicol and thiamphenicol. Like chloramphenicol and thiamphenicol, florfenicol is a potent inhibitor of microbial protein synthesis that exerts its effect via irreversibly binding the 50S subunit of the bacterial ribosome. However, florfenicol is not a substrate for acetyltransferase, the bacterial enzyme implicated in the development of resistance to chloramphenicol and thiamphenicol. Florfenicol has been shown to be active in vitro against common canine bacterial isolates, including *S intermedius* and *S aureus* with low resistance rates. Further, unlike chloramphenicol, florfenicol (when administered systemically) has not been reported to be associated with the risk for induction of human aplastic anaemia.[7–11] Given the frequency of use of ototopical treatments for OE, the developers sought an antibacterial agent that is rarely used parenterally in dogs, nor is listed as a critically important antimicrobial in human medicine.[12] Florfenicol was chosen as the antibacterial agent for this product as it meets these criteria.

Terbinafine is an antimycotic drug of the allylamine class, with demonstrated in vitro activity against a variety of fungal pathogens. Its fungicidal activity is attributed to inhibition of squalene epoxidation during sterol synthesis of fungal membranes.[13 14] Terbinafine has also been used systemically in the treatment of dermatophytosis in dogs and cats,[15 16] as well as in the treatment of canine *Malassezia* dermatitis.[17–19] In addition, topical terbinafine has been used successfully to treat dermatophytosis in mice,[20] and in a guinea pig model.[21] Of note, Sagit and others,[22] report no toxicity to the middle ear of rats when terbinafine was applied intratympanically.

Mometasone furoate is a potent, synthetic glucocorticoid that has been used in a variety of human and veterinary otic preparations. It is sometimes referred to as a 'soft potent glucocorticosteroid' because it is more potent than some older glucocorticoids, yet not as likely to cause systemic adverse reactions such as adrenal suppression.[1 23] Use of this steroidal agent reduces exudation and swelling associated with OE, thereby promoting drainage and ventilation, allowing for the antibacterial and antifungal agents to better exert their effects.

Most of data presented in this manuscript are from a *clinical study* of Otic Solution in canine OE. The *clinical study* was designed to test the efficacy and safety of Otic Solution in canine OE caused by bacteria and yeast under field conditions. Where appropriate, data from other studies conducted during the development of this product are included; key characteristics of these studies are included in the Materials and Methods, Results and online supplementary files sections.

MATERIALS AND METHODS

Clinical study

This was a multicentre, controlled, masked and randomised field study conducted over a period of 30 days, according to Good Clinical Practice guidelines. The study was conducted according to a Food and Drug Administration Center for Veterinary Medicine (FDA-CVM) concurred protocol, and informed consent was obtained from all owners of the study animals. The owner consent process included providing a general description of the Otic Solution, an overview of the investigational nature of the study and study requirements, as well as notification of the possibility that the owner's dog could be assigned to the negative control group. As with other registration studies for OE products, the primary efficacy criterion evaluated was clinical improvement. This was a registration study using a scoring system presented to and approved by the FDA-CVM before study initiation. Such studies are designed to demonstrate substantial evidence of effectiveness and safety using the product with a fixed treatment regimen. The result is that these studies may differ from treatment in a private practice or academic setting in which a clinician will typically treat until resolution of clinical signs and a return to normal otic cytology.

Study centres and animal selection

Dogs of various breeds with diagnosed bacterial and/or fungal OE, as confirmed by clinical signs and culture from an ear swab, were recruited from eight veterinary clinics in the USA. To assess eligibility, a detailed medical history and clinical examination were conducted (online supplementary table 1). A standard scoring system (online supplementary table 2) for evaluation of clinical signs associated with OE (ie, erythema, exudate, swelling and ulceration) was used, with a minimum score required for study enrolment as detailed below (see Study schedule and clinical scoring section). In dogs with bilateral OE, the right ear was designated as the study ear, although treatment of both ears was permitted.

Treatments

For the study, dogs were randomly assigned to receive Otic Solution or a vehicle control in a 2:1 ratio. The enrolment goal was a minimum of 140 dogs to receive Otic Solution and a minimum of 70 dogs to receive the vehicle control, to obtain a minimum of 100 evaluable treated cases and 50 evaluable control cases.

Patients received either a single dose of Otic Solution (16.6 mg/g florfenicol, 14.8 mg/ml terbinafine (equivalent to 16.6 mg/g terbinafine hydrochloride), 2.2 mg/g mometasone furoate) per each infected ear or received

vehicle control (an identical solution with the active ingredients omitted). Study treatment was administered on day 0, massaging the base of the dog's ear to encourage distribution of the product. No concomitant otic medications were allowed, and no systemic or topical antifungals or antibiotics, antihistamines, anti-inflammatory agents or corticosteroids were allowed.

Randomisation

Assignment to treatment group was made in presentation order using randomisation forms generated by the statistician with Statistical Analysis Software (SAS), with animals blocked in groups of three at each study site. All personnel at each veterinary clinic were masked as to treatment assignment. Treatments were in identical ampules, labelled with code letters.

Study schedule and clinical scoring

Dogs were evaluated at four different time points over a period of 30 days, on study days 0, 7, 14 and 30. At the initial visit on study day 0, physical, aural and otoscopic examination was performed, along with assignment of a clinical score upon evaluation of the following OE signs: erythema, exudate, swelling and ulceration. A standard scoring system (online supplementary table 2) for evaluation of these signs was used. Each of the four parameters was scored from 0 (unaffected) to 3 (most severely affected), resulting in a composite score of 0–12. A *clinical score* of at least 6 was required for study enrolment. Animals with a perforated tympanum (as assessed by visual otoscopy only) were excluded from the study. At this initial visit, an ear swab for bacterial and fungal culture was performed, as was a gross hearing assessment in which the clinician evaluated the dog's response to a hand clap out of the dog's line of sight. The ear was then cleaned by filling the aural canal with saline, massaging the base of the ear and wiping the accessible portion with cotton balls. This was followed by blood, serum and urine sample collection for clinical pathology. Follow-up visits were conducted on study days 7 and 14, which included aural and otoscopic exams, assignment of a clinical score and assessment of any adverse events. At the final follow-up visit (study day 30), a physical exam, hearing test (see hand clap procedure, above), aural and otoscopic exam were performed, along with assignment of a clinical score. Blood, serum and urine samples for clinical pathology were also collected at this final visit.

Microbiological culture and antibiotic/antifungal susceptibility testing

Bacterial/fungal culture and antibiotic/antifungal susceptibility testing were performed on day 0, and then again on day 30 only if clinical cure was not achieved. Investigators were instructed to insert the swab and rotate with moderate pressure, while targeting the junction of the vertical and horizontal ear canal. The swab was then inserted directly into transport media and shipped to the microbiology laboratory (Microbial Research, Fort Collins, CO, USA). At the microbiology lab, attempts were made to isolate the following pathogens: *M pachydermatis, S pseudintermedius, Pseudomonas aeruginosa, Proteus mirabilis, E coli* and beta-haemolytic *Streptococci*. Swab samples were streaked on agar plates and, after incubation, bacteria/yeast were identified and scored semiquantitatively based on an approximate number of presumptive colonies. A score of 1, 2, 3 or 4 was assigned to samples with approximately 1–10, 11–100, 101–1000 or >1000 presumptive colonies per agar plate, respectively. Bacterial isolates were identified and classified according to species, largely by means of the Maldi Biotyper (Bruker Daltonics, Billerica, MA, USA). For yeast identification, wet mounts of the isolates were observed for cellular morphology and growth characteristics. A score of 1 for a submitted specimen was indicative of pathogenicity if the culture was pure or if one of the other protocol-listed pathogens was present. Samples with more than two protocol-listed pathogens, or other organisms not listed in the protocol, were required to have a minimal score of 2 for the isolate to be considered pathogenic. For s*usceptibility testing*, identified pathogens were tested against florfenicol for bacteria or against terbinafine for yeast. This testing was conducted using the Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals and the Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts.[24 25] Minimal inhibitory concentration (MIC) results were interpreted to be the lowest concentration of antimicrobial agent that completely inhibited growth of the organism.

Efficacy criteria

The endpoint for efficacy was improvement in clinical score. *Treatment success* was defined as a clinical score of 3 or less on day 30, along with no individual score worsening on day 30 of assessment. If the day 7 score had not improved by at least 2 points from the day 0 score, or if the owner requested removal for perceived lack of improvement, the dog was removed from the study. Dogs were included in the efficacy evaluation if follow-up data were available after the initial visit and if there were no major protocol violations. Animals withdrawn from the study on days 7 or 14, and those whose clinical scores did not improve by at least 2 points and to less than or equal to 3 on day 30, were classified as *treatment failures*. Failures—a worsening in any of the clinical parameters (erythema, swelling, exudate, ulceration)—were subsequently treated as deemed appropriate by the attending veterinarian.

Safety assessments

Safety data collected and analysed include adverse events reported by the pet owner and/or investigator, as well as evaluation of haematology, urinalysis and hearing assessment results. Blood, serum and urine samples for clinical pathology were collected at the initial and final study visits. All cases receiving treatment, for which preclinical and postclinical chemistry, haematology and

/or urinalysis values were available, were included in the overall field safety analyses.

Statistical analyses

The primary analysis for effectiveness was a comparison of the proportions of treatment success in each group (Otic Solution or control) using a generalised linear mixed model. The statistical model included the ability to account for potential differences attributed to a site (ie, incorporating location/environment/veterinarian impression/interpretation) and the combination (interaction) of treatment group and site. Thus, the statistical model included 'Treatment' as a fixed effect and 'Site' and 'Treatment by Site' as random effects, allowing the model to account for potential site differences and better estimating the true treatment effect. A logit link function was employed in the model since the variable was binary in nature. The covariance structure 'Variance Component' along with the Kenward-Roger method of estimating the denominator degrees of freedom were used in the analysis. Full results of this statistical analysis are presented in the Results–clinical efficacy section.

All treated dogs were included in the safety evaluation. Clinical pathology variables (haematology, serum chemistry and urinalysis) were statistically evaluated using an analysis of covariance with the pretreatment value used as a covariate. The model included terms for the effects 'Treatment' and 'Site', as well as the interaction 'Treatment by Site'. The model term 'Site' and the interaction 'Treatment by Site' were treated as random effects in the model. The difference between treatment groups was evaluated at a two-sided 0.05 level of significance. All analyses were performed using SAS/STAT V.9 software.

Additional development studies

Target animal safety study

In this GLP (Good Laboratory Practices, as defined by the United States FDA 21CFR58) study, the safety of intra-aurally instilled Otic Solution was evaluated in three-month-old beagle dogs. Study medication was administered every two weeks for a total of three applications over a 28-day period, with four treatment groups of eight dogs each (online supplementary file 1).

Non-GLP ear flush study to evaluate systemic absorption and ear wash samples

This non-GLP study in 14 beagle dogs with normal ears was an exploratory study designed to characterise the rate and extent of systemic absorption and to provide a gross estimate of the duration of activity of florfenicol and terbinafine in the ear canal.

RESULTS

Clinical study

Study population

Two hundred and twenty-one dogs were enrolled in the study (initiated in November 2013, with last follow-up visit in May 2014): 146 received Otic Solution and 75 received the vehicle control (control) product. Various breeds were represented, including, most frequently, mixed breed dogs (30.3 per cent, 67/221), Labrador retrievers (11.8 per cent, 25/221), golden retrievers (7.6 per cent, 16/221) and Shih Tzus (6.2 per cent, 13/221). Dogs were evenly distributed within each treatment group by sex, and ranged in age from 17 weeks to 16 years, with weights ranging from approximately 5 to 122 pounds (table 1).

TABLE 1: Clinical study population: distribution by age, sex and bodyweight

	Otic Solution, cases enrolled	Control, cases enrolled	Total cases enrolled
Age			
≤1 year	5	6	11
>1 and ≤5 years	49	23	72
>5 and ≤10 years	68	36	104
>10 years	24	10	34
Total	146	75	221
Sex			
Female	6	8	14
Spayed female	67	31	98
Male	13	5	18
Castrated male	60	31	91
Total	146	75	221
Bodyweight			
≤10 lbs	12	3	15
>10 and ≤25 lbs	44	22	66
>25 and ≤50 lbs	32	11	43
>50 and ≤100 lbs	54	38	92
>100 lbs	4	1	5
Total	146	75	221

Clinical efficacy

Out of 221 dogs enrolled in the study, 38 were eliminated from the efficacy analysis due to failure to confirm microbial growth after enrolment, violation of inclusion/exclusion criteria, or other protocol deviation such as animals that required systemic antimicrobial therapy for other conditions. The remaining 183 dogs were included in the efficacy analysis: 120 in the Otic Solution group and 63 in the control group (fig 1). Regarding the assessment of treatment success, clinical cures were obtained in 87 of the 120 dogs receiving Otic Solution and 7 of the 63 dogs receiving the control. The efficacy of Otic Solution was 72.5 per cent, superior to the control (11.1 per cent) at p=0.0001 (table 2).

Bacterial and fungal isolates before treatment

Of the 311 samples submitted from ear swabs for pathogen isolation and identification, 264 were positive for

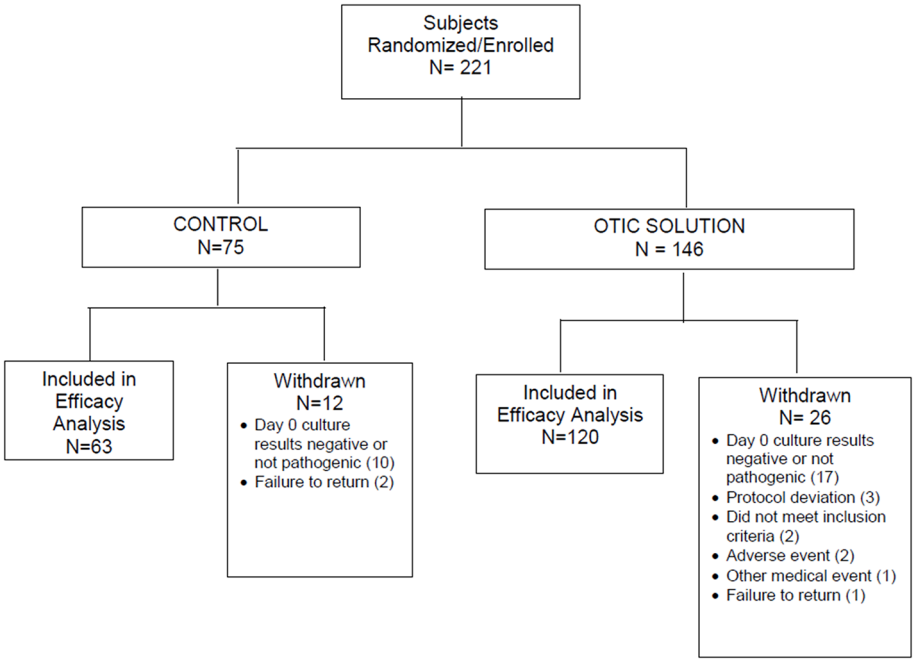

FIG 1: Disposition of study subjects: clinical study efficacy analysis.

one or more of the protocol-listed pathogens. *M pachydermatis* was the predominant organism, isolated from 224 (72 per cent) of the 311 ear swab samples. *S pseudintermedius* was isolated from 149 (48 per cent) of the 311 samples, *P aeruginosa* was isolated from 33 (11 per cent) of the 311 samples, *Streptococcus canis* was isolated from 31 (10 per cent) of the 311 samples, and *E coli, P mirabilis* and *Streptococcus dysgalactiae* were isolated from less than 10 per cent of the samples.

Antimicrobial susceptibility data, all cases

A total of 23 *E coli,* 9 *P mirabilis,* 44 *P aeruginosa,* 149 *S pseudintermedius,* 33 beta-haemolytic *Streptococcus* species and 222 *M pachydermatis* isolates were MIC-tested. Table 3 provides the MIC profile for each pathogen with florfenicol and terbinafine, including the MIC ranges, MIC_{50} and MIC_{90}.

Antimicrobial susceptibility data from evaluable cases, by treatment

Administration of Otic Solution was shown to be effective in treating cases of OE caused by *S pseudintermedius* (58 successful cases and 16 failures) and *M pachydermatis* (85 successful cases and 23 failures) (see table 4). Susceptibility data (MIC ranges and MIC_{50} values) for *S pseudintermedius* and *M pachydermatis* isolates obtained on day 0 and at study withdrawal did not show any correlation between higher MICs and treatment failure. This result was consistent whether data were analysed across the population or by individual case/animal.

For the additional pathogens from the study population listed in table 4, *E coli, P mirabilis, P aeruginosa* and beta-haemolytic *Streptococci* species, the number of treated cases did not meet the FDA minimum (10 successfully treated, evaluable cases for a given isolate) to consider effectiveness, and for some, the in vitro MICs were high. Thus, this Otic Solution is not approved for canine OE when these pathogens are involved. Other approved topical formulations with fluoroquinolones or aminoglycosides would be indicated in these situations.

Safety evaluations

Adverse events

No serious adverse events were reported during the study. The most common adverse events observed in the test product group were abnormal integument (six dogs), coughing/tracheobronchitis (two dogs), limping/arthritis (two dogs) and red eyes/conjunctivitis/blepharospasm

TABLE 2: Clinical study: effectiveness summary

Frequency of success/failure, by treatment*				
Treatment	**Success†**	**Failure‡**	**Success rate (%)**	**95% CI**
Otic Solution	87	33	72.5	64.51 to 80.49
Control	7	56	11.1	3.35 to 18.87

*Results of analysis indicate statistically significant difference in favour of the treatment group, p=0.0001.
†Treatment success is defined as a clinical score of 3 or less on day 30, along with no individual score worsening on day 30 of assessment.
‡Treatment failure is defined as withdrawal from the study on day 7 or 14, or clinical scores that did not improve by at least 2 points and to less than or equal to 3 on day 30 (ie, those in the effectiveness population that were not successes).

TABLE 3: MIC profile for bacterial and fungal isolates in the clinical study, all cases

		Min MIC (µg/ml)	Max MIC (µg/ml)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
Florfenicol	*Escherichia coli (n=23)*	4	64	8	16
	Proteus mirabilis (n=9)	4	8	4	8
	Pseudomonas aeruginosa (n=44)	64	>64	>64	>64
	Staphylococcus pseudintermedius (n=149_)	2	8	4	4
	Beta haemolytic Streptococci (n=33)	2	2	2	2
Terbinafine	*Malassezia pachydermatis (n=222)*	0.008	0.25	0.03	0.06

MIC, minimal inhibitory concentration.

(two dogs). Most of these events were also observed in the control group; therefore, none were considered attributable to Otic Solution. In addition, none of the dogs treated through study day 30 lost their ability to hear.

Laboratory variables

The haematology, serum chemistry and urinalysis results from the dogs treated with Otic Solution were compared with the results from the control group. The comparison

TABLE 4: Summary of antimicrobial susceptibility data from evaluable cases upon entry (day 0 (D0)) and withdrawal (WD), by treatment (clinical study)

	Otic Solution—treated cases, successful outcomes (D0)		Otic Solution—treated cases, failed outcomes (D0)		Otic Solution—treated cases, failed outcomes (WD)	
	MIC range (µg/ml)	(MIC_{50})*	MIC range (µg/ml)	(MIC_{50})*	MIC range (µg/ml)	(MIC_{50})*
Escherichia coli	8–32 (n=6)	8	4–16 (n=4)	16	8–16 (n=3)	16
Proteus mirabilis	4–8 (n=2)	NA	4 (n=1)	NA	8 (n=1)	NA
Pseudomonas aeruginosa	>64 (n=5)	NA	64 to >64 (n=7)	>64	>64 (n=5)	NA
Staphylococcus pseudintermedius	2–8 (n=58)	4	2–4 (n=16)	4	4 (n=9)	NA
Beta-haemolytic Streptococci species	2 (n=6)	NA	2 (n=4)	NA	2 (n=4)	NA
Malassezia pachydermatis	0.008–0.25 (n=85)	0.03	0.015–0.06 (n=23)	0.03	0.008–0.06 (n=5)	0.03
	Control—treated cases, successful outcomes (D0)		**Control—treated cases, failed outcomes (D0)**		**Control—treated cases, failed outcomes (WD)**	
	MIC range (µg/ml)	**(MIC_{50})***	**MIC range (µg/ml)**	**(MIC_{50})***	**MIC range (µg/ml)**	**(MIC_{50})***
E coli	NA (n=0)	NA	4–16 (n=5)	8	4–16 (n=4)	16
P mirabilis	NA (n=0)	NA	4–8 (n=2)	NA	4–8 (n=2)	NA
P aeruginosa	NA (n=0)	NA	64 to >64 (n=7)	>64	>64 (n=7)	NA
S pseudintermedius	4 (n=6)	NA	4 (n=26)	NA	2–4 (n=23)	4
Beta-haemolytic Streptococci species	NA (n=0)	NA	2 (n=10)	NA	2 (n=8)	NA
M pachydermatis	0.008–0.06 (n=8)	0.03	0.008–0.25 (n=47)	0.03	0.008–0.12 (n=41)	0.03

*If 10 or more isolates, MIC_{50} reflects the florfenicol (*E coli*, *P mirabilis*, *P aeruginosa*, *S pseudintermedius*,beta-haemolytic *Streptococci* species) or terbinafine (*M pachydermatis)* concentration that inhibited at least 50% of the isolates being described.
MIC, minimal inhibitory concentration.
NA is used here to denote where an MIC_{50} was not or could not be determined: i) for pathogens for which there were fewer than 10 isolates that completed the study (e.g *Proteus mirabilis),* or ii) pathogens for which fewer than 50% of evaluable cases experienced successful clinical outcomes.

showed that the only haematology variables with statistically significant differences were haemoglobin, mean corpuscular volume, red blood cell and white blood cell counts. The only serum chemistry variables with statistically significant differences were calcium, chloride, cholesterol, sodium/potassium and phosphorus. These haematology and chemistry differences were not considered clinically significant as all mean values were within the normal reference range for each value. There were no statistically significant differences in the urinalysis variables.

Additional development studies

GLP target animal safety study

None of the findings attributed to Otic Solution were considered adverse within the context of this safety study, and the study drug was considered to be well-tolerated (online supplementary file 1).

Non-GLP ear flush study

Systemic absorption

After a one-time ototopical dose of Otic Solution to dogs with normal (ie, non-inflamed) ears, minimal to no systemic absorption of each active ingredient was observed in the study dogs.

Ear wash samples

Quantification of florfenicol and terbinafine concentrations was performed on ear flushes of a small number of study dogs at each time point; regression analyses were then performed to guide timing of the final evaluation visit for the clinical trial.

DISCUSSION

In the clinical trial evaluating this new, single-dose combination treatment (Otic Solution) for canine OE, clinical improvement was observed in approximately 73 per cent of cases (v 11 per cent in the vehicle control group). This improvement persisted over a period of 30 days. Previously published trials for evaluating ototopical treatments of OE report a wide range of success rates, from approximately 40 to 95 per cent.[1 26–28] It is difficult to compare treatment success rates between studies because the criteria for clinical improvement and the time course for assessments differ; however, the 73 per cent treatment success rate noted with Otic Solution appears to be on par with the 40–95 per cent range cited above. Furthermore, it is of note that the dosing regimen for Otic Solution is less labour-intensive than those that require the pet owner to continue with administration of medication after initial application at the veterinary clinic.

In a clinical practice setting, re-evaluation during and before discontinuation of treatment is generally conducted with an otoscopic examination of the same or similar clinical criteria used in this trial: erythema, swelling, exudate and ulceration. Ideally, cytology of an otic sample collected from the junction of the vertical and horizontal canals is evaluated microscopically for a decrease in pathogens and ultimate return to normal flora. However, many clients when they perceive improvement in their dog's condition fail to return to the clinic for re-evaluation, making a product with residual activity desirable. Nevertheless, clients should be strongly encouraged to return for otitis rechecks. This is especially important in cases with a history of chronic recurrent otitis when after the current infection is resolved a switch to a long-term maintenance programme may be useful to prevent recurrence of inflammation and infection.

The combination of active ingredients in this otic formulation provides another option for clinicians to consider in the first-line treatment of OE. In an in vitro setting, the antibacterial and antifungal components of the formulation were effective at inhibiting growth of the two most common pathogens, *S pseudintermedius* and *M pachydermatis,* isolated from the ear swabs of dogs enrolled in this study. Specifically, florfenicol was effective at reducing pathogen growth, with an MIC_{90} of 4 µg/ml towards *S pseudintermedius*, while an MIC_{90} of 0.06 µg/ml was calculated for terbinafine towards *M pachydermatis*. Data from the ear flush study suggest that concentrations of florfenicol at 10 days (8.7 µg/ml) after administration of Otic Solution would still be at least twofold higher than its MIC_{90} for *S pseudintermedius,* and concentrations of terbinafine at this time point (4.8 µg/ml) would be 80 times higher than its MIC_{90} for *M pachydermatis*. Further, apart from *P aeruginosa* and *E coli,* the concentration of active ingredient in dog ear wash samples at days 5 and 10 remained well above the MICs observed for the remaining isolates. The doses of florfenicol and terbinafine in this new formulation are thus considered to be effective at achieving a significant reduction in growth of these pathogens. As these pathogenic isolates are representative of those observed in dogs with OE,[4 26 29] it seems reasonable to expect successful reduction of microbial growth upon treatment with Otic Solution.

Due to the multifactorial nature of OE, it is not always possible to predict clinical success based on MIC data alone, and supportive therapy targeting the underlying cause of the infection is often required.[30] However, in a general companion animal practice, where a conclusive diagnosis using cultures may not be feasible, the selection of an antimicrobial agent is frequently made empirically, and is further constrained by the availability of limited, fixed combinations. The practitioner must balance the efficacy profile of each active ingredient with any known risks to the patient. In the clinical trial, a one-time topical dose of Otic Solution into the dogs' affected ears generated both a favourable clinical response as well as a favourable safety profile with no adverse events of concern and no auricular toxicity. In addition, as determined during other referenced development studies, although minimal to no detectable levels of each active ingredient in Otic Solution were observed in serum samples over the seven-day period after administration of the study drug, each ingredient (i.e. florfenicol, terbinafine, and mometasone furoate) waspresent in ear flush samples at

clinically relevant concentrations. These results suggest that the effects of the product are primarily confined to the application site and that application at the proposed label dose is not expected to result in systemic absorption of significance for the constituent components. Finally, the addition of mometasone furoate to the Otic Solution affords a potent anti-inflammatory component with a favourable safety profile.

Due to the ever-present concerns regarding the development of antimicrobial resistance, the antibacterial component selected for this product is one that is not of critical importance in human medicine and seldom used parenterally in companion animals. Similarly, the selection of an allylamine antifungal component provides an alternate option for the treatment of dermatophytes, in the event significant resistance to azole class antifungal agents occurs. And while the impact of improper application and/or compliance by dog owners has not been well characterised, it is reasonable to anticipate that the in-hospital application of this product by trained professional staff will reduce treatment failures attributable to these causes. These factors, along with data from clinical studies reinforcing the efficacy and safety profile of this product, make Otic Solution an excellent first-line option for the treatment of OE.

Acknowledgements The authors would like to thank Sharon J Hirshey Dirksen, PhD, for her assistance in drafting the manuscript, and Louis G Luempert, III, PhD, for his assistance with the statistical analyses.Statistical analysis of this study was performed using Version 9 of the SAS System for Windows, Copyright(c) 2002-2010 by SAS Institute Inc., Cary NC, USA.

Funding The studies reported in this manuscript were funded by Piedmont Animal Health, Greensboro, NC, and Animal Health Division, Bayer, Shawnee Mission, KS

Competing interests The authors of this manuscript are employees of Bayer, Animal Health Division (Blake, Keil, Kwochka, Schofield) and Piedmont Animal Health (Palma).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement A summary of the pivotal study is available through FOI.

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