

Topical Antibacterial Agent for Treatment of Adult and Pediatric Patients With Impetigo: Pooled Analysis of Phase 3 Clinical Trials

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ABSTRACT

Ozenoxacin is a novel topical antibacterial agent with potent bactericidal activity against Gram-positive bacteria that has been developed as a 1% cream for treatment of impetigo. This article presents pooled results of pivotal clinical trials of ozenoxacin with the objective of evaluating the efficacy, safety, and tolerability of ozenoxacin 1% cream after twice-daily topical treatment for 5 days in patients with impetigo. A pooled analysis was performed of individual patient data from two multicenter, randomized, double-blind, vehicle-controlled phase 3 registration studies conducted in patients with impetigo. Both clinical trials followed a similar methodology. Patients were randomized 1:1 to ozenoxacin or vehicle. One trial included retapamulin as an internal control. Efficacy was measured using the Skin Infection Rating Scale and microbiological culture. Safety and tolerability were evaluated. Ozenoxacin demonstrated superior clinical success versus vehicle after 5 days of therapy, superior microbiological success versus vehicle after 2 days of therapy, and was safe and well-tolerated. Ozenoxacin showed superior clinical and microbiological response versus vehicle in children as young as 2 months of age, and adults, with impetigo.

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INTRODUCTION

Impetigo is the most common bacterial skin infection in children, although it can occur at any age.[1-6] As impetigo is highly contagious, the condition is of particular concern in daycare centers and schools.[7] Disease control is important to limit outbreaks, relieve symptoms, minimize scarring due to excoriation, and prevent rare but serious complications such as glomerulonephritis.[8] This approach provides the rationale for antibiotic treatment of impetigo.[9,10] More rapid clearance of skin lesions reduces the risk of contagion, which is particularly important in children. Clinical practice guidelines generally advocate use of topical antibacterials for localized impetigo, and oral antibiotics for patients with extensive lesions and those with systemic infection.[11]

Staphylococcus aureus is the main causative pathogen of impetigo although *Streptococcus pyogenes* is sometimes involved.[2,10,12,13] Resistance rates to commonly used topical antibiotics, such as mupirocin, are reported to be as high as 81%.[14] Similarly, significant resistance rates of *S. aureus* to fusidic acid have emerged in a number of countries, potentially limiting its overall efficacy.[15,16] Growing antibiotic resistance is a particular concern for patients who present with empirically managed diseases such as impetigo[17] as patients are often treated without the benefit of culture and sensitivity results to guide appropriate care. New antibacterial agents with different modes of action to current drugs, and with activity against resistant strains, are clearly desirable.

Ozenoxacin is a topical antibiotic that has demonstrated potent bactericidal activity against pathologically relevant Gram-positive organisms, particularly Staphylococci and Streptococci. Topical ozenoxacin has negligible systemic ab-

sorption[18] and exhibits an expanded spectrum against methicillin-, mupirocin-, and ciprofloxacin-resistant strains of *S. aureus*.[19-21] Ozenoxacin may therefore represent an important localized empirical therapy in the treatment of impetigo.

The clinical efficacy and safety of ozenoxacin 1% cream was evaluated in children and adults with impetigo in two randomized, vehicle-controlled, phase 3 clinical trials.[22,23] A pooled analysis of these pivotal studies, which was conducted to confirm the results in a larger sample, is provided herein.

PATIENTS AND METHODS

Study Designs

Both pivotal phase 3 clinical trials originating data for this pooled analysis were multicenter, randomized, vehicle-controlled, parallel-group, double-blind, superiority clinical trials comparing ozenoxacin cream and vehicle cream in patients with a clinical diagnosis of impetigo.[22,23] One study included a retapamulin-treated arm as an internal control and, due to the different appearance of the two formulations, was investigator-blinded for retapamulin versus vehicle comparison.[22]

The studies were conducted at 53 centres in seven countries (Germany, Romania, South Africa, Ukraine, Spain, Russia, and USA) in accordance with ethical principles set out in the Declaration of Helsinki and the ICH Harmonized Tripartite Guideline for Good Clinical Practice. The protocol and informed consent were approved by Institutional Review Boards at each study site and all subjects (or their legal guardian) provided written informed consent prior to entry.

Study Population

Patients aged 2 months or older included in this pooled analysis had a clinical diagnosis of impetigo with a total affected area at baseline not exceeding 100 cm^2. For patients < 12 years old, the total area could not exceed 2% of the body surface area. Exclusion criteria have been described previously in the individual studies.[22,23]

Impetigo severity at baseline was assessed according to the Skin Infection Rating Scale (SIRS) used in each study.[22,23]

Study Procedures and Assessments

Subjects were randomized to receive ozenoxacin 1% cream or vehicle (or retapamulin in Study 1 only). Patients were allocated unique identification numbers. Randomization was performed by an independent statistician using an interactive web response system and patients were stratified into age subsets.

During the 5-day treatment period, patients were instructed to apply a thin layer of study drug (a fingertip unit [approximately 0.5 g], which covers the maximum extension of 100 cm^2) to the baseline affected area(s) twice daily. Ozenoxacin and vehicle did not differ in color, smell or consistency and were presented in identical aluminium tubes. Since retapamulin is formulated as an ointment, it was administered in investigator-blinded fashion.

Assessments were conducted at four visits: baseline (Visit 1), day 3-4 (Visit 2), end of therapy (day 6-7; Visit 3), and follow-up (day 10-13; Visit 4). A telephone call was arranged 24 to 36 hours after the start of study medication for early evaluation of lesion evolution.

At each visit, the number and location of affected areas, and total area of impetigo were assessed. The affected area was graded using the SIRS evaluation.

The definition of clinical success at the end of therapy (Visit 3) was consistent with draft guidance on requirements for generics of mupirocin for treatment of impetigo and secondarily infected traumatic lesions issued in June 2010 by the US Food and Drug Administration (FDA),[24] and was established as follows:

- SIRS scores of 0 for exudates/pus, crusting, and pain, and a SIRS score ≤ 1 for erythema/inflammation (subjects in Study 1); or SIRS scores of 0 for exudates/pus, crusting, and itching/pain, and a SIRS score ≤ 1 for erythema/inflammation (subjects in Study 2).

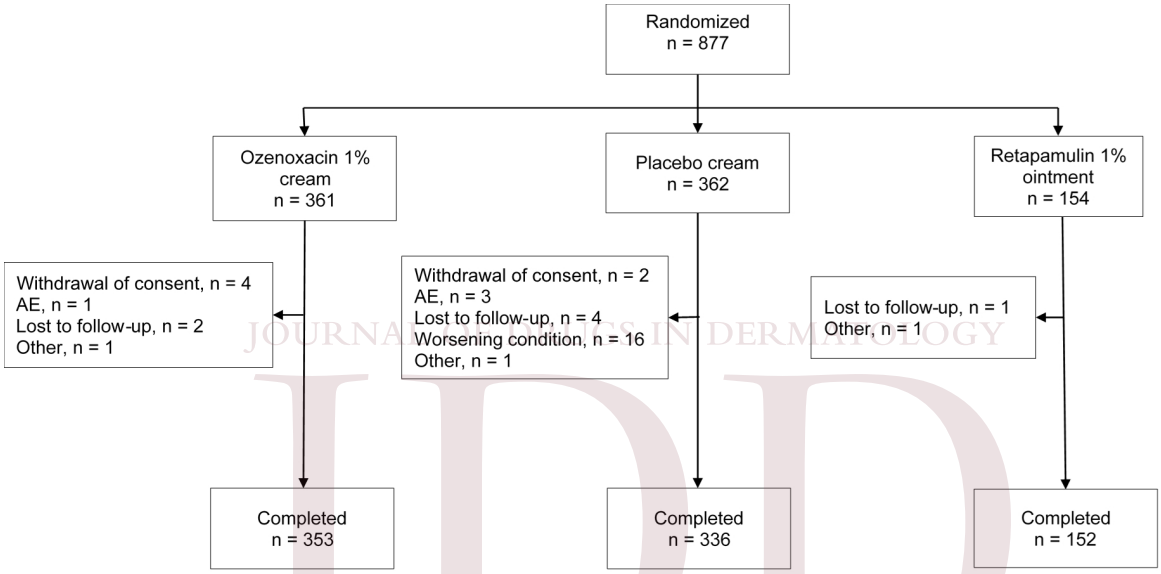
A patient was classified as a clinical success if he/she fulfilled the appropriate SIRS criteria and no additional antimicrobial therapy of the baseline affected area(s) was necessary.

To make the results more comparable to those for other approved topical drugs marketed for treatment of impetigo, clinical success at the end of therapy was assessed considering not only clinical cure but also clinical improvement reflecting previously accepted methodology for other topical antibiotics approved for impetigo.[25-32] This definition of clinical success was previously defined[26,27] as follows:

- Total absence of treated lesions (lesion extension = 0) OR treated lesions have become dry without crusts compared to baseline (SIRS = 0 for exudate and for crusting), OR improvement (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy is necessary.

The microbiological response was evaluated at all study visits by taking microbiological samples from the affected area identified at baseline, provided that culturable material was present. All specimens were sent to a central laboratory for identification of pathogen/s. Characterisation of possible antibacterial resistance was evaluated for specimens collected at Visit 1.

FIGURE 1. Patient flowchart for the pooled analysis of two pivotal phase 3 trials of ozenoxacin. AE, adverse events.



Microbiological success was defined as the absence of the original pathogen(s) from Visit 1 in the culture of specimens taken from the baseline affected area. In the absence of successful microbial culture of a specimen, microbiological success was considered to be clinical cure or improvement.

Study Endpoints

The primary efficacy endpoint was the clinical response (clinical success or clinical failure) at the end of therapy (Visit 3) in the intent-to-treat clinical (ITTC) population.

Key secondary efficacy endpoints were clinical response (clinical success and improvement or clinical failure) at Visit 3, and microbiological response at Visits 2 and 3.

Evaluation of safety was based on adverse events, vital signs and physical examination.

Microbiological susceptibility of pathogens identified at Visit 1 to ozenoxacin, methicillin (oxacillin), ciprofloxacin, retapamulin, mupirocin and fusidic acid, and the presence of Panton-Valentine Leukocidin (*PVL*) and Phenol Soluble Modulin (*PSM*) genes, were also analyzed.

Statistical Analysis

Data for patients from the two pivotal studies were pooled.

For all efficacy analyses, the primary treatment comparison was to test the superiority of ozenoxacin versus vehicle in the ITTC (clinical response) and intent-to-treat bacteriological (ITTB; microbiological response) populations. The ITTC population was defined as all randomized patients. The ITTB population was defined as all randomized patients who had a pathogen identified at study entry. The *P*-value of the chi-square test (without continuity correction) and corresponding 95% asymptotic (Wald) confidence interval (CI) for the difference in success rates was calculated. Only outcomes for clinical success and clinical failure were used to calculate the difference in success rates, CI, and *P*-value. Patients classified as 'unable to determine' were excluded from the analysis.

Data for patients treated with retapamulin (Study 1) were shown if no statistical differences in response (according to Fisher's exact test) were observed between the two studies. In the variable clinical response (see Table 2) differences of more than 15% ($P<0.05$) were observed in both treatments (ozenoxacin and placebo) between Study 1 and 2. For this reason, results of the primary efficacy endpoint for retapamulin in Study 1 are not comparable to the pooled results for ozenoxacin and placebo. The same applies to the variable microbiological response at Visit 2 and Visit 3 (see Table 3).

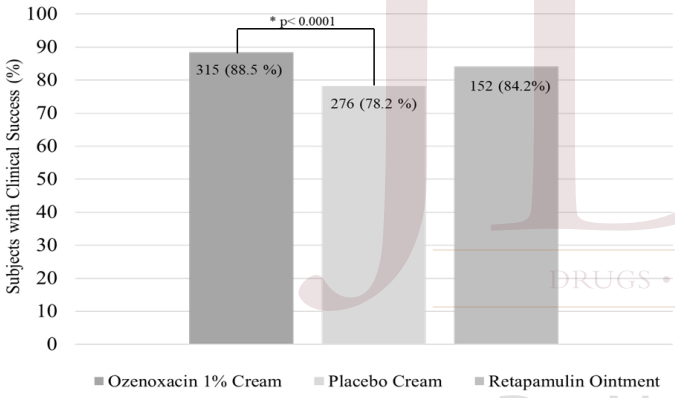
RESULTS

Patients

This pooled analysis includes individual data for 877 patients enrolled in the phase 3 studies. Patients were from South Africa (n = 390); US (n = 212, including Puerto Rico [n = 46]); Germany (n = 125); Romania (n = 63); Russia (n = 57); Ukraine (n = 27); and Spain (n = 3). Enrolled subjects had been randomized to receive ozenoxacin 1% cream (n = 361), placebo cream (n = 362), or retapamulin 1% ointment (n = 154). A total of 36 subjects (4.1%) discontinued the study prematurely: 16 due to a worsening

FIGURE 2. Clinical response at end of therapy, using combined criteria of clinical success in the intent-to-treat clinical (ITTC) population. The difference in success rates (ozenoxacin – placebo) was 0.103 (95% asymptotic (Wald) confidence interval [CI]: 0.048-0.157; *P*< 0.001 for chi-square test without continuity correction). Only outcomes for clinical success and clinical failure were used to calculate the difference in success rates, CI, and *P*-value. The remaining patients were classified as unable to determine and were excluded from the analysis. The retapamulin arm was used as an internal control and no statistical comparison was performed. *Clinical success was defined as a total absence of treated lesions (lesion extension = 0) or treated lesions became dry without crusts compared to baseline (Skin Infection Rating Scale = 0 for exudate and for crusting), or improvement (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy was necessary.*

Figure 2: Clinical success at the end of therapy (day 6-7, Visit 3)



condition; seven were lost to follow-up; six withdrew consent; four discontinued due to adverse events (AEs); and three discontinued for other reasons. All 16 subjects who discontinued due to worsening condition were in the placebo group, and three of four subjects who discontinued due to AEs were in the placebo group (Figure 1).

Subjects' demographics and baseline characteristics are summarised in Table 1. The demographics and baseline characteristics of subjects enrolled in the phase 3 studies were representative of patients with impetigo in the general population.

Efficacy Results

Clinical response

The clinical success rate in the ITTC population at the end of therapy for the pooled analysis was 47.3% in the ozenoxacin 1% group versus 31.4% in the vehicle group (*P*<0.001; Table 2). The proportion of subjects who achieved clinical cure and improvement at the end of therapy was 88.5% in the ozenoxacin 1% group, 78.2% in the placebo group (*P*<0.0001) and 84.2% in the retapamulin group (no statistical comparison, used as internal control only; Figure 2).

Microbiological response

The proportion of subjects in the ozenoxacin group (n = 279) who achieved eradication or presumed eradication of all evaluated pathogens was significantly higher than vehicle-treated patients (n = 271) at Visit 2 (80.4% *vs* 52.3%; *P*<0.0001) and Visit 3 (90.8% *vs* 69.8%; *P*<0.0001; Table 3).

Activity against resistant organisms including methicillin-resistant S. aureus

Thirty-six patients in the ozenoxacin group had resistant *S. aureus* strains identified at baseline, with demonstrable resistance to at least one of the tested antibacterials (methicillin [oxacillin], ciprofloxacin, retapamulin, mupirocin and fusidic acid); and two patients had resistant *S. pyogenes* strains to at least one of these antibacterial agents. All patients with resistant infections achieved clinical cure or improvement at Visit 3, including 11 of 11 patients with mupirocin-resistant *S. aureus*, and 10 of 10 patients with methicillin-resistant *S. aureus.* Ozenoxacin demonstrated similar clinical and microbiological success rates irrespective of the presence of *PVL* and *PSM* genes in the *S. aureus* isolates.

Safety and Tolerability

Five (0.6%) of 875 treated subjects (one patient in each study was randomized but not treated and thus not included in the safety population) experienced six AEs that were considered by investigators to be possibly or probably study drug-related. These were: worsening of pre-existing rosacea and seborrheic dermatitis (both events were reported in a single adult subject in the ozenoxacin 1% cream group); dermatitis and skin tightness (reported in one subject each in the placebo cream group); and application site pain and urticaria (reported in one subject each in the retapamulin 1% ointment group). As none of the AEs considered study drug-related occurred in more than one subject, no patterns or safety signals were identified.

DISCUSSION

Impetigo is a bacterial skin infection caused mainly by *S. aureus* and *S. pyogenes*, with highly contagious lesions that can spread rapidly by direct contact.[2] Rapid, effective treatment is required to reduce autoinoculation and contagion so as to minimize outbreaks and avoid potential complications. Growing resistance rates to commonly utilized antibiotics such as mupirocin[33,34] is becoming a major concern worldwide.[35,36] These factors have driven the need to identify new agents with different modes of action that exhibit activity against resistant strains.

Ozenoxacin is characterized structurally as a non-fluorinated quinolone and has demonstrated bactericidal activity against

TABLE 1.

Demographics and Baseline Characteristics (ITTC Population)

	Ozenoxacin 1% cream (n = 361)	Placebo cream (n = 362)	Retapamulin 1% ointment (n = 154)	Overall (n = 877)
Mean ± SD age (years)	17.6 ± 18.0	17.9 ± 18.0	15.1 ± 15.0	17.3 ± 17.5
Median (min, max)	10.0 (0.3, 79.6)	10.1 (0.2, 83.0)	9.0 (2.0, 71.0)	10.0 (0.2, 83.0)
Age categorized, n (%)				
≥ 2 months to < 12 years old	207 (57.3)	207 (57.2)	95 (61.7)	509 (58.0)
≥ 12 years to < 18 years old	43 (11.9)	40 (11.0)	15 (9.7)	98 (11.2)
≥ 18 years to < 65 years old	101 (28.0)	104 (28.7)	41 (26.6)	246 (28.1)
≥ 65 years old	10 (2.8)	11 (3.0)	3 (1.9)	24 (2.7)
Male gender, n (%)	211 (58.4)	194 (53.6)	92 (59.7)	497 (56.7)
Predominant race, n (%)				
Caucasian	180 (49.9)	202 (55.8)	50 (32.5)	432 (49.3)
Black or African-American	130 (36.0)	115 (31.8)	79 (51.3)	324 (36.9)
Asian	17 (4.7)	15 (4.1)	3 (1.9)	35 (4.0)
Native American	0	2 (0.6)	0	2 (0.2)
Mixed Race	34 (9.4)	28 (7.7)	22 (14.3)	84 (9.6)
Mean ± SD height (cm)	136.6 ± 32.9	137.7 ± 31.1	132.1 ± 30.1	136.2 ± 31.7
Mean ± SD weight (kg)	43.7 ± 28.1	43.7 ± 27.2	37.3 ± 24.7	42.6 ± 27.2
Mean ± SD body surface area (m2)	1.26 ± 0.55	1.26 ± 0.52	1.14 ± 0.50	1.24 ± 0.53
Nonbullous impetigo, n (%)	303 (83.9)	294 (81.2)	125 (81.2)	722 (82.3)
Mean ± SD number of affected areas	2.7 ± 2.9	2.6 ± 2.8	3.5 ± 4.3	2.8 ± 3.2
Mean ± SD total affected area (cm^2)	9.9 ± 14.8	10.6 ± 15.4	12.1 ± 22.4	10.5 ± 16.6
Mean ± SD total affected area (% BSA)	0.090 ± 0.139	0.085 ± 0.104	0.096 ± 0.149	0.089 ± 0.128

ITTC: intent-to-treat clinical; SD: standard deviation, BSA: body surface area.

TABLE 2.

Clinical Response at Visit 3 (Primary Efficacy Endpoint) (ITTC Population)

	Ozenoxacin 1% cream (n = 361)	Placebo cream (n = 362)
Visit 3 (day 6-7, end of therapy), n	357	354
Clinical success, n (%)[a]	169 (47.3)	111 (31.4)
Clinical failure, n (%)[b]	188 (52.7)	243 (68.6)
Difference in success rates (ozenoxacin – placebo)	0.159	
95% CI[c]	0.089 - 0.231	
P-value[d]	<0.001	

ITTC: intent-to-treat clinical; CI: confidence interval.

Only outcomes for clinical success and clinical failure were used to calculate the difference in success rates, CI, and *P*-value. The remaining patients were classified as unable to determine and were excluded from the analysis.

[a]Clinical success was defined as total absence of treated lesions: Skin Infection Rating Scale (SIRS) scores of 0 for exudates/pus, crusting, and pain, and a SIRS score ≤ 1 for erythema/inflammation (subjects in study 1); or SIRS scores of 0 for exudates/pus, crusting, and itching/pain, and a SIRS score ≤ 1 for erythema/inflammation (subjects in study 2).

[b]Improvement (defined as >10% decrease in total SIRS score compared with baseline, not fulfilling the criteria of individual SIRS scores for cure), and failure, were both considered clinical failure.

[c]95% asymptotic (Wald) CI for the difference in success rates.

[d]*P*-value of the chi-square test (without continuity correction).

TABLE 3.

Microbiological Response at Visit 2 and Visit 3 (ITTB Population)

	Ozenoxacin 1% cream (n = 279)	Placebo cream (n = 271)
Visit 2 (day 3-4), n	271	256
Microbiological success, n (%)[a]	218 (80.4)	134 (52.3)
Microbiological failure, n (%)	53 (19.6)	122 (47.7)
Difference in success rates	0.281	
95% CI[b]	0.204-0.358	
P-value[c]	<0.0001	
Visit 3 (day 6-7, end of therapy), n	261	248
Microbiological success, n (%)[a]	237 (90.8)	173 (69.8)
Microbiological failure, n (%)	24 (9.2)	75 (30.2)
Difference in success rates	0.21	
95% CI[b]	0.143-0.278	
P-value[c]	<0.0001	

ITTB: intent-to-treat bacteriological; CI: confidence interval.

Only outcomes for microbiological success and microbiological failure were used to calculate the difference in success rates, CI, and *P*-value. The remaining patients were classified as unable to determine and were excluded from the analysis.

[a]*Overall microbiological success was defined as eradication, a composite of documented eradication (absence of the original pathogen from the post-treatment culture of the specimen obtained from the original site of infection) and presumed eradication (complete resolution of signs and symptoms associated with the absence of culturable material).*

[b]95% asymptotic (Wald) CI for the difference in success rates.

[c]*P*-value of the chi-square test (without continuity correction).

the most common Gram-positive pathogens associated with skin and soft tissue infection including sensitive and resistant *S. aureus* strains.[37] Ozenoxacin also exhibited greater inhibitory activity than other quinolones for bacterial DNA gyrase and topoisomerase IV, critical enzymes for the transcription and replication processes of bacterial DNA.[19,20]

In two phase III regulatory registration studies, ozenoxacin demonstrated early bacteriological eradication after 2 days of treatment, and a significantly superior clinical and microbiological response compared to placebo after 5 days of treatment.[22,23] In contrast to studies of previously approved topical drugs for treatment of impetigo, the ozenoxacin studies used the SIRS to assess lesion severity and clinical response as per FDA guidance.[24] The pre-planned test for internal validity demonstrated that retapamulin was significantly superior to placebo and produced a clinical success rate similar to that recorded for ozenoxacin.

As clinical response criteria utilized in the ozenoxacin studies were more stringent than those used in previous studies of topical anti-infectives for impetigo, clinical success rates appeared to be lower than those reported for retapamulin, mupirocin, and sodium fusidate. Data analysis using the classical methodology, including clinical improvement in addition to clinical cure, showed clinical success rates of 88.5% for ozenoxacin, 84.2% for retapamulin, and 78.2% for placebo ($P<0.001$ vs ozenoxacin). These figures are consistent with clinical success rates reported for other topical therapies.[10,25-27] Thus, differences in methodology must be considered when comparing efficacy rates across antibacterials.

In terms of microbiological response, ozenoxacin produced earlier microbiological clearance than placebo after two days of therapy, as highlighted by success rates of 80.4% for ozenoxacin versus 52.3% for placebo ($P< 0.0001$). This could be clinically beneficial in terms of reducing the likelihood of autoinoculation and contagion.

CONCLUSION

Pooled data from two pivotal phase 3 studies confirm that ozenoxacin is a rapid and effective treatment for impetigo. It exhibits an expanded spectrum against methicillin-, mupirocin- and ciprofloxacin-resistant bacteria.[20,37] By decreasing the symptoms of skin infection, ozenoxacin can reduce the spread of pathogens and lower infection transmission. The consistent clinical and bacteriological effects and favourable safety profile of ozenoxacin 1% cream in children as young as 2 months of age support its position as an important therapeutic option for patients with impetigo.

DISCLOSURES

Nuria Albareda and Ilonka Zsolt are employees of Ferrer Internacional. S.A. The remaining authors have no conflicts of interest to declare.

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