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Abstract

Background: This study aimed to assess the efficacy of MP-AzeFlu (a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate in a single spray) in children with seasonal allergic rhinitis (SAR) and explore the importance of child symptom severity assessment in paediatric allergic rhinitis (AR) trials.

Methods: A total of 348 children (4–11 years) with moderate/severe SAR were randomized into a double-blind, placebo-controlled, 14-day, parallel-group trial. Efficacy was assessed by changes from baseline in reflective total nasal symptom score (rTNSS), reflective total ocular symptom score (rTOSS) and individual symptom scores over 14 days (children 6–11 years; n = 304), recorded by either children or caregivers. To determine whether a by-proxy effect existed, efficacy outcomes were assessed according to degree of child/caregiver rating. Moreover, total Paediatric Rhinitis Quality of Life Questionnaire (PRQLQ) score was compared between the groups.

Results: A statistically superior, clinically relevant efficacy signal of MP-AzeFlu versus placebo was apparent for PRQLQ overall score (diff: −0.29, 95% CI −0.55, −0.03; p = 0.027), but not for rTNSS (diff: −0.80; 95% CI: −1.75; 0.15; p = 0.099). However, as the extent of children's self-rating increased, so too did the treatment difference between MP-AzeFlu and placebo; MP-AzeFlu provided significantly better relief than placebo for rTNSS (p = 0.002), rTOSS (p = 0.009) and each individual nasal and ocular symptom assessed (except rhinorrhoea; p = 0.064) when children mostly rated their own symptoms.

Conclusions: MP-AzeFlu is an effective treatment for AR in childhood. Caregivers are less able than children to accurately assess response to treatment with available tools. A simple paediatric-specific tool to assess efficacy in AR trials in children is needed.

Allergic rhinitis (AR) occurs in 8.3% of children aged 6–7 years, rising to 14.6% in older children (those aged 13–14 years) (1). Its impact is routinely underestimated, but is far-reaching, negatively affecting children's overall physical and emotional health, daily activities, quality of sleep and productivity at school (2). Due to this high burden of disease,

there is an ethical duty to ensure provision of effective pharmacotherapy by conducting and reporting good quality efficacy and safety trials in children with AR. To that end, applications for new medicinal products in the EU (since 2007) and the United States (since 2003 according to the Pediatric Research Equity Act) must include the results of studies conducted in the paediatric population, in compliance with an agreed paediatric investigation plan (3).

Intranasal corticosteroids (INS) are widely used to treat AR in children. Their efficacy is well established in both adults and adolescents with seasonal allergic rhinitis (SAR) (4, 5), but inconsistent effects have been observed in school children (6), without a clear dose–response relationship (6–8). Indeed, a Cochrane review concluded that the evidence for the effectiveness of INS for the treatment of intermittent and persistent AR in children is 'weak and unreliable', and the reduction in symptom severity as assessed in these trials could not be confirmed with the data provided (6). Difficulties associated with analysing data from paediatric AR trials include the high placebo effect in randomized controlled trials (RCTs) in all groups, and the smaller effect size traditionally observed in children as compared to adults (4, 7).

Furthermore, there are few specific instruments to assess the efficacy of anti-allergic treatments in children. The Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) has been developed specifically for children (9), but has been used in relatively few RCTs (10, 11). In paediatric AR trials, efficacy is still assessed using end-points originally designed for adult use (i.e. reflective total nasal and ocular symptom scores). The extensiveness, complexity and subjective nature of these scores leads to them often being recorded by caregivers rather than by children themselves. However, comparisons of the results between children and caregiver assessments have not been made to validate this approach. An allergic rhinitis and its impact on asthma (ARIA)-GA2LEN article proposed that paediatricians and methodologists should analyse current RCTs in 5- to 11-year-old children to make a comparison between adolescent/adult and children studies (pharmacologic and immunotherapy) (12).

MP-AzeFlu (Dymista®, Meda, Solna, Sweden) comprises an intranasal antihistamine (azelastine hydrochloride (AZE)) an INS (fluticasone propionate (FP)) and a novel formulation delivered in a single spray. Its efficacy and safety is well established in adults and adolescents with SAR (13, 14) and those with chronic rhinitis (i.e. perennial AR (PAR) or non-allergic rhinitis) (15, 16), providing faster and more complete symptom control than monotherapy with an intranasal antihistamine or INS. MP-AzeFlu has recently been approved for paediatric use in the United States by the Food and Drug Agency (FDA). Interestingly, although the FDA acknowledged that the reflective total nasal symptom score (rTNSS) remains the gold standard primary end-point in AR trials, the challenges of caregiver-reported assessment were noted.

As part of a pivotal phase III study assessing the efficacy and safety of MP-AzeFlu in 6- to 11-year-old children with SAR (NCT01915823), different outcomes for efficacy were analysed in-depth to provide new insights into the importance of paediatric symptom severity assessment when assessing efficacy in paediatric AR trials.

Methods

Study design and hypothesis

This was a randomized, double-blind, multicentre (35 investigational sites in the United States) placebo-controlled, parallel-group, 14-day trial, carried out in children (aged 4 to <12 years old) with moderate/severe SAR (July 2013 to February 2014). Ethics approval was obtained from Chesapeake Research Review Inc, Columbia MD. Informed consent (from caregiver) and paediatric informed consent (from children 7 years of age and older) were obtained prior to initiation of any study-related procedure. The study was conducted in accordance with good clinical practice.

Symptom severity was assessed using changes from baseline in rTNSS, reflective total ocular symptom score (rTOSS), reflective total of 7 symptom scores (rT7SS) and individual symptom scores and could be recorded by either children or caregivers. Quality of life (QoL) was assessed using the PRQLQ and was completed by physicians and children, but without input from caregivers. To determine whether a by-proxy effect existed, overall and individual nasal and ocular symptom scores were assessed according to degree of child/caregiver rating. Moreover, PRQLQ was also compared between the two groups.

Participants

Inclusion criteria and exclusion criteria are presented in the online supplement. Briefly, male and female children ≥4 to <12 years of age (at screening visit) with a history of SAR and positive skin prick test showing hypersensitivity to prevailing pollen were enrolled. Participants were required to have a rTNSS ≥6 and reflective congestion score ≥2 on the first day of placebo lead-in.

Interventions and timing

The study comprised a 3–7 days, single-blind, placebo lead-in period and a 14-day treatment period, with 3 study visits on days 1, 8 (±1 day) and at end of trial (Day 15 + 3 days). On Day 1, eligible children were randomized in a 1:1 ratio to treatment with either MP-AzeFlu nasal spray or placebo, both administered as 1 spray/nostril bid, separated by approximately 12 h (total daily dose of AZE: 548 μg, FP: 200 μg). Children or their caregivers recorded nasal and ocular symptom scores in an eDiary twice daily prior to dosing with study medication. Children >6 years old also completed the PRQLQ at the investigator site on Day 8 and Day 15.

Efficacy variables

The primary end-point was change from baseline in morning and evening rTNSS (max score: 24) over the 14-day treatment period in children aged 6 to 11 years. Secondary efficacy

end-points included change from baseline in rTOSS (max score 18), rT7SS (i.e. rTNSS + rTOSS; max score; 42), and individual nasal and ocular symptoms (each scored 0 to 3; AM and PM) over the entire double-blind period in the same age group (online supplement). Daily change from baseline in rTNSS, rTOSS and rT7SS were also assessed secondarily. Change in the PRQLQ total score was assessed from baseline to days 8 and 15.

Safety variables

Safety end-points included child/caregiver-reported adverse events (AE; by incidence, type and severity – see online supplement), focused nasal examination and vital signs measurements.

Sample size, randomization and blinding

Details are provided in the online supplement text.

Statistical analyses

Children were randomized and stratified by age group (i.e. 4–5 years, 6–8 years, and 9–11 years). As pre-specified in the protocol, data from 6- to 11-year-olds were analysed using inference statistics. Data from 4- to 5-year-olds were considered as exploratory only and summarized using descriptive statistics. Primary and secondary end-points, including PRQLQ for children aged 6 to 11 years were assessed using a repeated-measures analysis of covariance (ANCOVA) model with treatment day (for PRQLQ: visit), treatment group and age group as fixed effects and baseline as a covariate. p-values ≤0.05 were judged to be significant. Primary and secondary end-points were also analysed *post hoc* according to degree of child assessment (details provided in the results section). A change from baseline in morning and evening rTNSS of at least 50% was considered and defined as a substantial response and analysed by Kaplan–Meier estimates and log-rank tests.

Results

Children

A total of 348 children were randomized. Children aged ≥4 to <6 years old (n = 44) were excluded from the efficacy analyses as pre-specified in the statistical analysis plan and agreed with the FDA. Efficacy is presented for the pre-defined pivotal group only (6–11 years; n = 152 in each group in the intent-to-treat (ITT) population). Children's disposition is provided in the online supplement (Figure S1). Discontinuation rate was very low (n = 2 in each group). Baseline characteristics were similar in the MP-AzeFlu and placebo groups (Table 1).

Table 1 Child demographic and baseline characteristics in those children aged ≥6 to <12

Characteristic	MP-AzeFlu (n = 152)	Placebo (n = 152)
Age, years,	9.0 ± 1.6	9.0 ± 1.6
≥6 years to <9 years	59 (38.8)	60 (39.5)
≥9 years to <12 years	93 (61.2)	92 (60.5)
Gender		
Male	86 (56.6)	80 (52.6)
Race		
Black/African American	43 (28.3)	39 (25.7)
White	100 (65.8)	107 (70.4)
Other or mixed	9 (5.9)	6 (3.9)
Duration of SAR, years	6.1 ± 2.6	6.2 ± 2.4
rTNSS (AM + PM)	18.4 ± 3.5	18.0 ± 3.2
rTOSS (AM + PM)	9.9 ± 4.5	9.5 ± 4.7
Total PRQLQ score	2.6 ± 1.2	2.7 ± 1.2

Values are presented as mean ± standard deviation or n (%).
SAR, seasonal allergic rhinitis; rTNSS, reflective total nasal symptom score; rTOSS, reflective total ocular symptom score; PRQLQ, Paediatric Rhinitis Quality of Life Questionnaire.

Child-reported quality of life (children aged 6–11 years)

A superior efficacy signal of MP-AzeFlu versus placebo was apparent in the QoL outcome. By Day 8, treatment with MP-AzeFlu induced the clinically relevant improvement in PRQLQ overall score (17) of −0.62, which was not the case for placebo (−0.45; diff: −0.17; 95% CI −0.38, 0.04; p = 0.118) (Fig. 1). By Day 15, MP-AzeFlu-treated children experienced a statistically superior and clinically relevant improvement in their QoL (−0.95) compared with placebo-treated children (−0.65; diff −0.29; 95% CI −0.55, −0.03; p = 0.027) (Fig. 1). MP-AzeFlu also provided greater improvement than placebo in each of the domain scores of the PRQLQ, reaching significance by Day 15 for the activity limitation (diff −0.43; 95% CI −0.73, −0.12; p = 0.007) and nose symptoms (diff: −0.35; 95% CI −0.69, −0.02; p = 0.036) domains (Figure S2).

Overall nasal symptoms (children aged 6–11 years)

There was no statistically significant difference between MP-AzeFlu and placebo (ITT population) for overall change

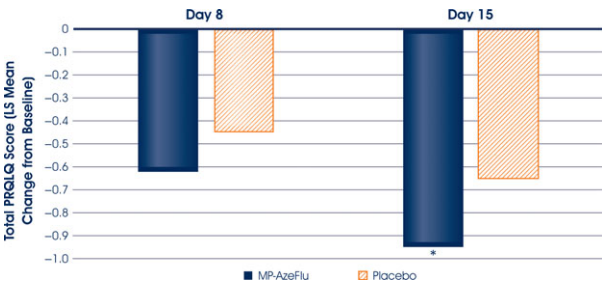

Figure 1 Least square (LS) mean change from baseline in Paediatric Rhinitis Quality of Life Questionnaire (PRQLQ) total score following treatment with MP-AzeFlu (n = 152) or placebo (n = 152), both 1 spray/nostril bid, for 14 days in children aged ≥6 to 11 years with moderate/severe seasonal allergic rhinitis. *Diff: −0.29; 95% CI −0.55, −0.03; p = 0.027.

from baseline in rTNSS (AM + PM). Children treated with MP-AzeFlu experienced a −3.70 pt reduction from baseline compared to −2.90 in the placebo group (diff: −0.80; 95% CI: −1.75; 0.15; p = 0.099) (Table 2). However, statistical significance over placebo was noted for sneezing (diff −0.32; 95% CI: −0.59, −0.04; p = 0.025) and approached significance for eye watering (diff: −0.26; 95% CI −0.52, 0.0002; p = 0.051) (Table S1). Furthermore, older children (i.e. those aged ≥9 and <12 years) treated with MP-AzeFlu (n = 93) experienced a −3.75 change from baseline in their overall rTNSS compared with −2.62 point reduction in the placebo group (n = 92) (diff: −1.13; 95% CI: −2.21, −0.05; p = 0.040). Similarly, those in the per protocol population (PPP) who received MP-AzeFlu (n = 128) experienced a −3.99 pt reduction from baseline in rTNSS compared to −2.78 pt reduction observed in placebo children (n = 136), a difference of −1.21 (95% CI −2.24, −0.13; p = 0.022). Exclusions from the PPP were primarily due to poor dosing compliance (i.e. <70% compliance on days 1–14) or due to poor compliance with rTNSS recording in the diary (i.e. <9 days rTNSS data for days 2–14).

Efficacy outcome (children vs. caregiver sensitivity analysis)

Since PRQLQ was assessed by children themselves at the investigational site, whereas rTNSS was assessed by either children or their caregivers, it was hypothesized that lack of statistical significance in the primary efficacy end-point (i.e. change from baseline in overall rTNSS [AM + PM]) was a consequence of rater assessment bias rather than lack of efficacy. Further evidence to support that hypothesis is the statistically significant difference between treatments in overall rTNSS change from baseline observed in older children (aged ≥9 to <12 years) who more likely assessed their own symptoms.

Table 2 Comparison of the efficacy of 14 days treatment with MP-AzeFlu or placebo (both 1 spray/nostril bid) in children aged 6 to 11 years with moderate/severe SAR in the ITT population and according to degree of child self-rating

	All children (n = 304)		Child self-rating <10% (n = 157)		10% ≤child self-rating ≤90% (n = 65)		Child self-rating >90% (n = 82)	
End-point	MP-AzeFlu - placebo	p-value	MP-AzeFlu - placebo	p-value	MP-AzeFlu - placebo	p-value	MP-AzeFlu - placebo	p-value
rTNSS	−0.80	0.099	−0.29	0.6722	−1.14	0.2281	**−2.18**	**0.0020**
rTOSS	−0.53	0.143	−0.19	0.6862	−0.48	0.4713	**−1.34**	**0.0090**
rT7SS	−1.34	0.093	−0.49	0.6662	−2.05	0.1951	**−3.41**	**0.0036**
Nasal congestion	−0.13	0.318	0.03	0.8589	−0.08	0.7328	**−0.45**	**0.0174**
Nasal Itch	−0.20	0.140	−0.19	0.2702	−0.17	0.5109	**−0.54**	**0.0039**
Rhinorrhoea	−0.09	0.505	−0.01	0.9705	−0.26	0.2876	−0.37	0.0640
Sneezing	**−0.32**	**0.025**	−0.04	0.7982	−0.31	0.2092	**−0.93**	**<0.0001**
Ocular itch	−0.19	0.172	−0.08	0.6053	0.12	0.6320	**−0.60**	**0.0008**
Ocular watering	−0.26	0.051	−0.18	0.2400	0.00	0.9835	**−0.51**	**0.0098**
Ocular redness	−0.11	0.389	0.04	0.7791	−0.35	0.0771	**−0.38**	**0.0355**

Data shown in bold with shading: statistically significant superiority of MP-AzeFlu versus placebo.
Child self-rating <10%: child assessment <10% of time (i.e. mostly caregiver); 10% ≤child self-rating ≤90%: child assessment ≥10% but ≤90% of the time (i.e. mixture of child and caregiver assessment); Child self-rating >90%: child assessment >90% of time (i.e. mostly children).
ITT, intent to treat; rTNSS, reflective total nasal symptom score; rTOSS, reflective total ocular symptom score; rT7SS, reflective total of 7 symptom scores; SAR, seasonal allergic rhinitis.

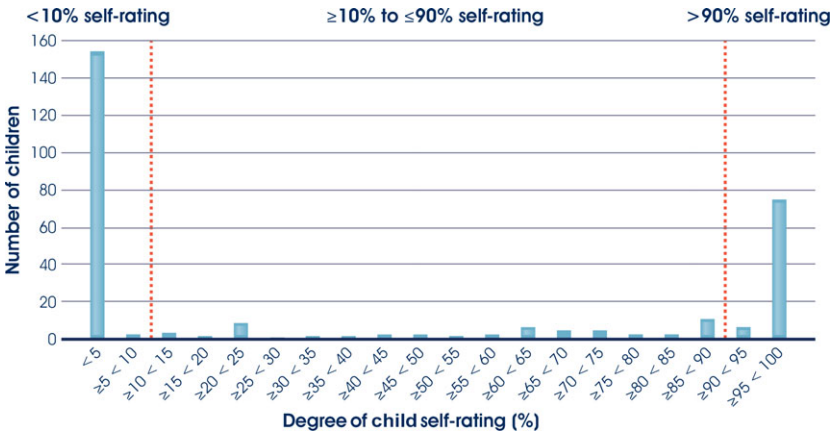

Figure 2 Distribution of child symptom severity assessment rating.

A rater sensitivity analysis was conducted to test this hypothesis. Distribution of degree of child assessment is shown in Fig. 2. Three groups were identified: (i) child assessment <10% of time (i.e. mostly caregiver; n = 157); (ii) child assessment ≥10% but ≤90% of the time (i.e. mixture of child and caregiver assessment; n = 65); and (iii) child assessment >90% of time (i.e. mostly children; n = 82). This sensitivity analysis revealed greater treatment difference between MP-AzeFlu and placebo with increasing degree of child self-rating (Table 2). As the extent of child self-rating increased, so too did the treatment difference between MP-AzeFlu and placebo. In the group which comprised <10% child self-rating (n = 157), no significant difference was noted between MP-AzeFlu and placebo for any efficacy outcome assessed. Conversely, in the group which comprised >90% child self-rating (n = 82), children treated with MP-AzeFlu experienced significantly better relief than those treated with placebo from their overall nasal symptoms (TNSS; p = 0.002), their overall ocular symptoms (TOSS; p = 0.009), overall T7SS (p = 0.0036), and from each individual nasal and ocular symptoms assessed (with the exception of rhinorrhoea p = 0.064) (Table 2). Daily change from baseline in rTNSS (AM + PM) according to degree of self-rating is shown in Fig. 3a–c. A similar pattern of

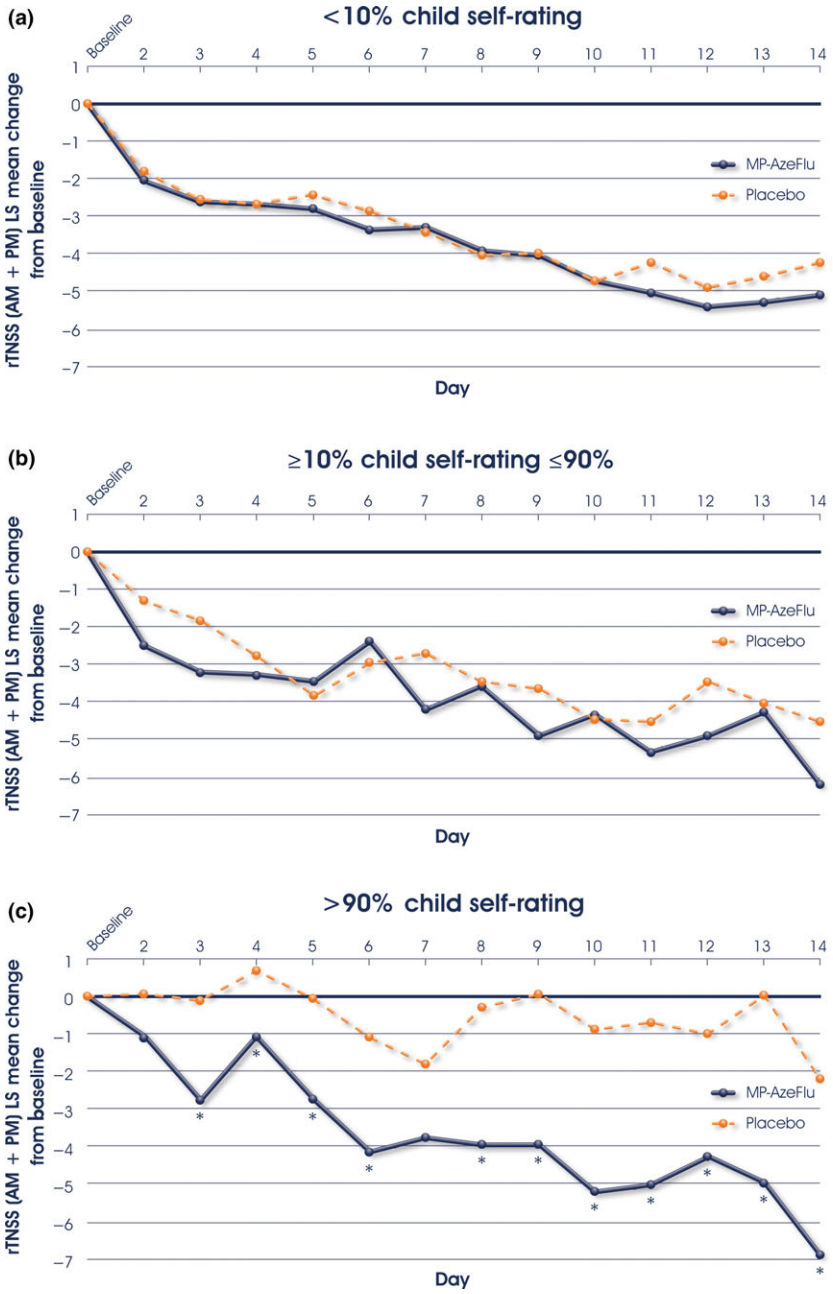

Figure 3 Least square (LS) mean change from baseline in reflective total nasal symptom score (rTNSS; AM + PM) per day according to degree of child self-rating following treatment with MP-AzeFlu or placebo, both 1 spray/nostril bid, for 14 days in children aged 6 to 11 years with moderate/severe SAR. *p ≤ 0.040 vs. placebo.

increasing effect with increasing degree of child rating was observed for the ≥50% response data (Fig. 4a–c). Baseline characteristics of children in each subgroup are shown in Table S2.

Safety

All children (i.e. 4–11 years; n = 348) were included in the safety analysis. Twenty-eight children (16.2%) in the MP-AzeFlu-group and 23 children (13.1%) in the placebo group reported at least one treatment emergent adverse event (TEAE). Of these, 15 (8.7%) and 6 (3.4%) were considered to be treatment-related adverse events (TRAE) in the MP-AzeFlu and placebo groups, respectively. The most common TRAE in the MP-AzeFlu group was dysgeusia (n = 7; 4.0% vs. n = 0 in the placebo group). Epistaxis occurred with similar incidence in the MP-AzeFlu (n = 6; 3.5%) and placebo groups (n = 5; 3.4%). All of these TRAE were considered by investigators to be 'mild' in severity. The percentage of children with TEAEs leading to discontinuation was the same in each group: 1 child (0.6%) per group. No serious adverse events were reported.

Neither MP-AzeFlu nor placebo was associated with any significant focused nasal examination finding. The proportion of children with moderate or severe mucosal oedema or nasal discharge decreased over time. Slight improvements in mucosal erythema were evidenced among the MP-AzeFlu-treated children. There were no clinically relevant abnormal vital sign

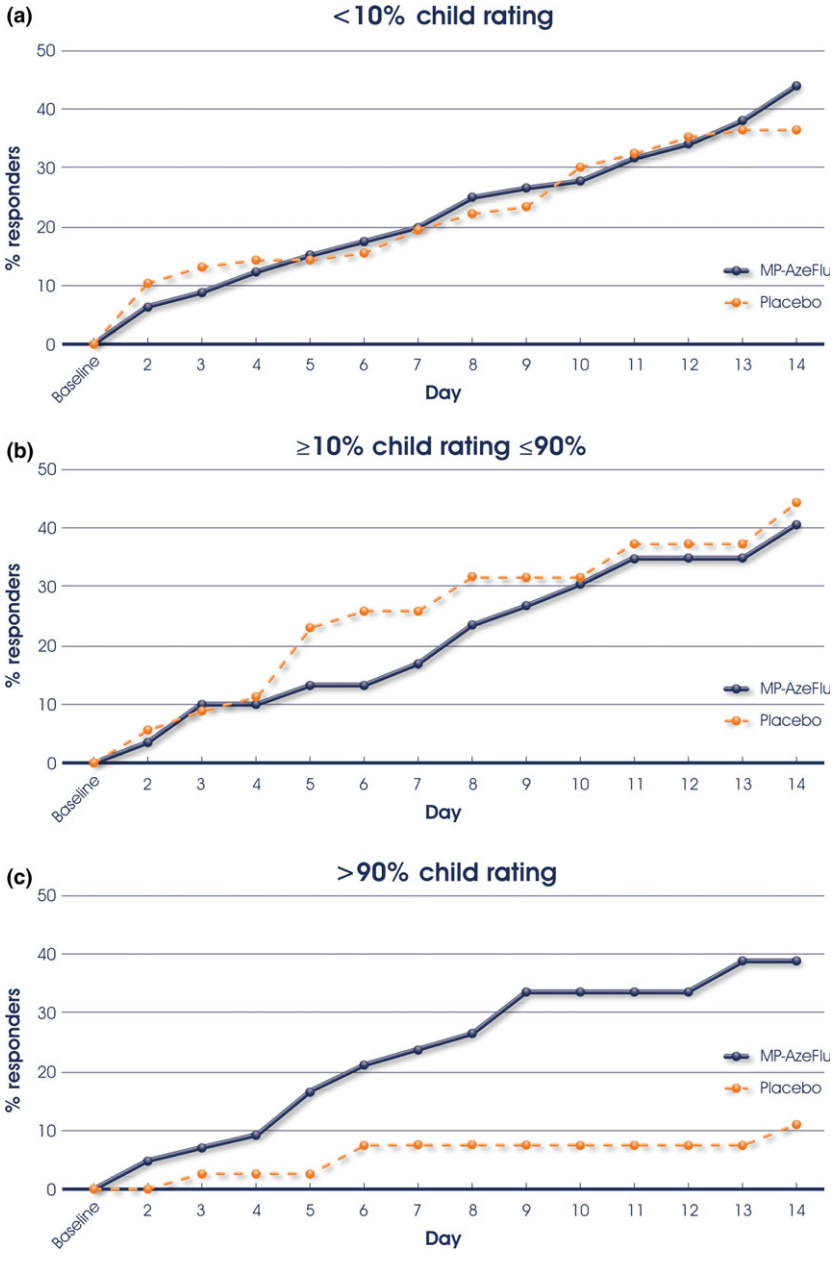

Figure 4 Time to achieve ≥50% change from baseline in reflective total nasal symptom score (rTNSS) according to degree of child self-rating in children aged 6 to 11 years with moderate/severe SAR. MP-AzeFlu versus placebo for <10% child self-rating: p = 0.36; ≥10% to ≤90% child self-rating: p = 0.69; >90% child self-rating: p = 0.0065.

measurements from baseline to end of the study in either treatment group.

Discussion

AR carries a high symptomatic and societal burden for sufferers, but especially so for children who experience significant negative impact on their QoL, daily functionality, sleep quality and productivity (2, 18). More effective pharmacological interventions would reduce this burden. MP-AzeFlu provides twice the overall nasal and ocular symptom relief as an INS and more complete rapid symptom control in both adults and adolescents (13–15). The results of this study confirm its efficacy in children, with an effect size (when children rate their own symptoms) comparable to that seen in adult studies (13), providing the evidence needed to achieve approval for paediatric use in the United States. However, assessment of efficacy was confounded by factors particular to paediatric AR trials, most notably, the practice of caregiver by-proxy assessment of children's symptom severity. The results presented here show that children's and caregivers' symptom assessments cannot be assumed to be the same, and emphasize the importance of using paediatric-generated data when possible.

This study is important as for the first time the efficacy of MP-AzeFlu has been shown in children with SAR. It included a large paediatric population, with a representative cross section of ages (4–5 years (n = 44), 6–8 years (n = 119) and 9–11 years (n = 185)) and evaluated efficacy in three ways ((i) QoL, (ii) symptom score reduction (both nasal and ocular) and (iii) time to achieve a clinically relevant response). However, although QoL was assessed using a paediatric-specific and validated tool (i.e. by PRQLQ), symptom relief was assessed by rTNSS (which is not validated in either adults or children). Future paediatric AR trials would benefit from the inclusion of a paediatric-specific and validated symptom severity assessment tool, such as a simple visual analogue scale (VAS). Such a VAS has been used in other AR trials (19), correlates well with rhinitis QoL questionnaire scores and rTNSS (20) and is sensitive enough to discriminate according to severity (21) and effectiveness of pharmacological interventions (22). The generalizability of these data is an inherent limitation of all RCTs (23) since inclusion and exclusion criteria must be in agreement with FDA and EMA guidelines.

In the present study, children treated with MP-AzeFlu experienced a clinically relevant and statistically significant improvement in their QoL compared with those children treated with placebo by Day 15. Impact on QoL clearly resonates with children, describes the burden of their disease in a way that is understandable to them and more importantly represents the views of children themselves (being completed at the investigational site without the presence of caregivers). However, the complexity of the PRQLQ, the fact that it collects reflective data for the past 7 days and that it must be filled in during clinic visits makes it an unsuitable tool for everyday use. MP-AzeFlu also reduced children's overall nasal symptom burden to a greater degree than placebo, but this did not reach statistical significance for the ITT population, most likely compromised due to the fact that caregivers rated symptom severity for children by proxy.

Superiority over placebo was achieved, however, for older children (those >9 years), and in the PPP as well as for the more 'objective' symptoms of sneezing (which can be heard) and eye watering (which can be seen). However, the more 'hidden' symptoms (such as congestion) proved more difficult for caregivers to accurately assess. This substantially reduced the study sensitivity; caregivers underestimated the MP-AzeFlu response and overestimated the placebo response. However, when children rated their own symptoms MP-AzeFlu provided significantly better symptom relief for all nasal and ocular efficacy parameters assessed (with the exception of rhinorrhoea, which approached statistical significance).

The same lower treatment effect and confounder has been reported in other paediatric trials (24–26). For example, Danell and colleagues showed that children (with asthma, rhinitis or eczema) reported more symptoms than their parents, concluding that symptoms of allergic disease should be reported by children themselves, from the age of 11 years (24). Poor agreement between children and parents for asthma drug use has also been noted (25). Finally, a recently published ARIA-GALEN statement recognized that the efficacy of sublingual immunotherapy (SLIT) for AR observed in RCTs may be less in children than in adults (12), possibly due in part to lack of a paediatric-specific assessment tool. Indeed, when using an easy overall efficacy assessment tool (e.g. a 4-point symptom severity rating scale from 0 (no symptoms) to 3 (severe symptoms)), MP-AzeFlu provided significantly greater AR symptom relief than FP in children aged ≥6–12 years with AR (27).

In conclusion, MP-AzeFlu is an effective treatment option for AR in childhood. Caregivers are less able than children to accurately assess response to treatment (at least with available tools). A simple and paediatric-specific tool to assess efficacy in AR trials in children is urgently needed.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Child disposition.

Figure S2. Least square (LS) mean change from baseline in Individual Paediatric Rhinitis Quality of Life Questionnaire (PRQLQ) domain scores following 15 days treatment with MP-AzeFlu (n = 152) or placebo (n = 152), both 1 spray/nostril bid in children aged ≥6 to 11 years with moderate/severe seasonal allergic rhinitis.

Table S1. rTNSS, rTOSS, rT7SS and individual nasal and ocular symptom scores at baseline and change from baseline following 14 days treatment with either MP-Aze-Flu or placebo in children (aged 6–11 yrs) with moderate/severe SAR.

Table S2. Child demographic and baseline characteristics by child self-rating group in those children aged 6 to 11 years.