Intranasal Triamcinolone and Growth Velocity

David P. Skoner, MD\textsuperscript{a, b}, William E. Berger, MD, MBA\textsuperscript{c}, Sandra M. Gawchik, DO\textsuperscript{d, e}, Akbar Akbary, MD\textsuperscript{f}, Chunfu Qiu, PhD\textsuperscript{g}

abstract

BACKGROUND: Inadequate designs and conflicting results from previous studies prompted the US Food and Drug Administration to publish guidelines for the design of clinical trials evaluating the effects of orally inhaled and intranasal corticosteroids on the growth of children. This study conformed to these guidelines to evaluate the effect of triamcinolone acetonide aqueous nasal spray (TAA-AQ) on the growth of children with perennial allergic rhinitis (PAR).

METHODS: This randomized, double-blind, placebo-controlled, parallel-group, multicenter study evaluated the effect of once-daily TAA-AQ (110 $\mu$g) on the growth velocity (GV) of children aged 3–9 years with PAR by using stadiometry at baseline (4–6 months), during treatment (12 months), and at follow-up (2 months). Hypothalamus-pituitary-adrenal (HPA) axis function was assessed by measuring urinary cortisol levels. Details of adverse events were recorded.

RESULTS: Of 1078 subjects screened, 299 were randomized, and 216 completed the study (placebo, 107; TAA-AQ, 109). In the primary analysis (modified intent-to-treat: placebo, 133; TAA-AQ, 134), least-squares mean GV during treatment was lower in the TAA-AQ group (5.65 cm/year) versus placebo (6.09 cm/year). The difference (-0.45 cm/year; 95% confidence interval: -0.78 to -0.11; $P = .01$), although clinically nonsignificant, was evident within 2 months of treatment and stabilized thereafter. At follow-up, the GV approached baseline (6.70 cm/year) in the TAA-AQ group (6.59 cm/year) and decreased slightly in the placebo group (5.89 cm/year vs 6.06 cm/year at baseline). No HPA axis suppression was observed.

CONCLUSIONS: By using rigorous Food and Drug Administration–recommended design elements, this study detected a small, statistically significant effect of TAA-AQ on the GV of children with PAR.

WHAT’S KNOWN ON THIS SUBJECT: Previous trials reported no significant effect of triamcinolone acetonide aqueous nasal spray on growth velocity of children with perennial allergic rhinitis. However, they did not conform to Food and Drug Administration guidelines for evaluating effects of intranasal corticosteroids on growth.

WHAT THIS STUDY ADDS: This is the first published study consistent with the 2007 Food and Drug Administration–recommended study design evaluating growth velocity in children aged 3–9 years with perennial allergic rhinitis treated with triamcinolone acetonide or placebo for 12 months.
Allergic rhinitis (AR), a chronic inflammatory condition, affects 10% to 40% of children globally.1–4 Intranasal corticosteroids (INCs) are the most efficacious treatment option in relieving nasal congestion and controlling frequent symptoms and are the treatment of choice for persistent AR.5,6 Nasacort (Sanofi-aventis, Bridgewater, NJ; microcrystalline suspension of triamcinolone acetonide aqueous nasal spray [TAA-AQ]) has been marketed in the United States for nearly 2 decades and is approved for treating nasal symptoms of both perennial AR (PAR) and seasonal AR in adults and children. Double-blind, placebo-controlled studies have shown that TAA-AQ is effective and well tolerated in children.7 Each actuation delivers 55 μg TAA-AQ. The starting dose is 110 μg (1 spray/ nostril) once daily (QD) in children aged 2–12 years, which can be titrated up to 220 μg QD for children aged 6–12 years.7

Starting in 1998, the US Food and Drug Administration (FDA) required the labeling of all inhaled corticosteroids (nasal and oral) to carry warnings and precautions of potential systemic effects, including growth retardation. However, growth studies in children using inhaled corticosteroids yielded varying results, probably because different study designs were used. In 2007, the FDA released a guidance document8 outlining the characteristics of study designs to reduce variability and/or potential bias in the estimates of differences in growth velocity (GV) between treatment groups. Key recommendations include a sample size of 150 to 200 patients per treatment arm, adequate characterization of baseline GV, stadiometric measurements, and identification of catch-up growth effects through follow-up.9 Previous studies conforming to these criteria have been conducted in patients with asthma treated with orally inhaled corticosteroids.9–11

Although studies with TAA-AQ in children with AR have examined its efficacy and safety12 as well as GV,13,14 the long-term effect of TAA-AQ on growth has not been assessed in randomized controlled trials. This study, designed per the FDA guidance recommendations, evaluates the difference in the GV of children aged 3–9 years with PAR treated with intranasal TAA-AQ or placebo for 12 months.

METHODS

Study Design

This randomized, double-blind, placebo-controlled, parallel-group, multicenter study comprised a 4- to 6-month screening/baseline period, a 12-month double-blind treatment period, and a 2-month follow-up period (Fig 1). The study, approved by the Schulman Associates Institutional Review Board, was conducted per the globally accepted standards of Good Clinical Practice (GCP), the Declaration of Helsinki, and local regulations. Written informed consent was obtained from the parents/legal guardians of the participants.

Subjects

Male subjects aged 3 to ≤9 years + 0 days at the first screening visit (4–6 months before randomization) and ≤9 years + 120 days at the randomization visit or female subjects aged 3 to ≤8 years + 0 days at the first screening visit and ≤8 years + 120 days at the randomization visit were eligible for inclusion (girls can enter puberty earlier than boys; hence, the different age cutoffs per FDA guidance for industry8). Subjects had to be prepubertal (ie, stage 1 of the Tanner classification of sexual maturity) at screening and randomization visits, have at least a 1-year history of PAR (with or without seasonal AR) and a positive skin test (prick or intradermal) to a perennial allergen, be symptomatic (daily morning instantaneous total nasal symptom score [TNSS] ≥4 out of 12) on any 4 of the last 7 consecutive days immediately before and including the morning of the randomization day, and have a height within the 3rd and 97th percentiles per the National Center for Health Statistics (NCHS) at screening and randomization visits.

At the baseline visit (2 to 6 weeks before randomization), subjects were excluded if their bone age, assessed by radiograph of the left hand and wrist, was outside ±1.5 years of their chronological age or if they showed an
abnormal 24-hour urinary free cortisol level. The Supplemental Information includes detailed exclusion criteria.

Interventions

After screening and baseline visits, all eligible subjects were randomly assigned (1:1; double-blinded) via an interactive voice response system to receive either TAA-AQ or a matching placebo. Randomization was stratified by age group (3–5 vs 6–9 years at screening) and gender. TAA-AQ (total daily dose of 110 µg) or placebo was administered intranasally QD in the morning during the 12-month double-blind treatment period. Details of allocation, randomization, blinding, and concomitant medication are included in the Supplemental Information. Children’s Claritin syrup (Schering-Plough, Kenilworth, NJ; loratadine; 5 mg/5 mL) was provided as rescue medication to control AR symptoms and could be used on an as-needed basis throughout the study.

Assessments and Outcomes

Primary End Point

The primary end point was GV during the double-blind treatment period. The GV of a subject in a time interval, such as the double-blind treatment period, was calculated as the slope of a regression line to fit all age-height data points in the interval. At each visit, the subject’s height was measured 3 times while barefoot by using a Harpenden stadiometer. If the difference among the triplicate readings was ≥0.4 cm, an additional 2 measurements were taken. The average of all measurements recorded was considered as the height of the subject at that visit.

Secondary End Points

Pharmacodynamic variables included GV percentiles (3rd, 25th, 75th, and 97th) of each subject and their change from baseline to the double-blind treatment period, GV during the first 4 months of the treatment period, and GV during screening/baseline and follow-up.

Efficacy variables were changes from baseline in instantaneous TNSS and 4 individual nasal symptom scores, subject and physician global evaluations of efficacy, and use of rescue medication (see Supplemental Information).

Safety

Safety assessment included the incidence of adverse events (AEs); 24-hour urinary free cortisol and urine cortisol/creatinine ratio; vital signs, weight, and BMI; and other safety variables (physical examination, Tanner classification, and bone age; see Supplemental Information).

Statistical Analyses

Considering the wider age range of the pediatric population in this study than in previous studies,10–12 the sample size was determined such that the total width of the 95% confidence interval (CI) for the difference in the mean GV based on the modified intent-to-treat (mITT) population (ie, all subjects in the intent-to-treat population who had at least 3 postrandomization visits with recorded height measurements during the double-blind treatment period; other populations are defined in the Supplemental Information) would be <0.90 cm/year. From a blinded interim review of the study data, the common SD of the GV in the mITT population was estimated to be 1.717 cm/year. Accordingly, a sample of 224 subjects (112 subjects per treatment arm) in the mITT population was required and, consequently, 274 randomly assigned subjects were needed. The mITT population comprised at least 82% of all randomly assigned subjects. The mean difference (95% CI) in GV between TAA-AQ and placebo groups was estimated by using an analysis of covariance model with terms of treatment arm, age group, gender, and baseline GV.

GV during the first 4 months of the double-blind treatment period was analyzed, similar to the primary variable for the mITT and per-protocol (PP) populations. Other secondary end points pertaining to GV and efficacy were summarized by descriptive statistics for each treatment group of the mITT and PP populations. Further details are provided as Supplemental Information.

Safety analyses were performed on the safety population, which included all subjects who took at least 1 dose of TAA-AQ or placebo (except for 5 subjects at 2 GCP-noncompliant sites). Incidences of treatment-emergent AEs (TEAEs) were summarized by treatment group. Summary statistics of all laboratory and vital sign variables (values and changes from baseline) were calculated for each assessment visit by treatment group. Bone age categories were tabulated by treatment group and visit.

RESULTS

Of the 1078 subjects screened at 81 study centers in the United States, 299 were randomly assigned and 216 (TAA-AQ, 109; placebo, 107) completed the study (study period: March 14, 2007, to October 12, 2011).

Among the 82 subjects who discontinued (41 in each treatment group), protocol violation (31.7%) and subject discretion (20.7%) accounted for >50% of the discontinuations. One subject in the TAA-AQ group and 3 in the placebo group discontinued due to AEs (Supplemental Table 5). Figure 2 shows subject disposition.

Baseline characteristics of the randomly assigned subjects (57.9% boys, 75.3% whites) are shown in Table 1. The median age at randomization was 6.67 years (range: 3.4–10.1 years).

Study medication was taken, as directed (1 spray/nostril per day), by 112 (76.2%) and 113 (77.4%) subjects in the placebo and TAA-AQ populations.
groups, respectively, for at least 274 days (~75% of a year).

Pharmacodynamic Results

In the mITT population, a lower GV was observed during the double-blind treatment period in the TAA-AQ group than in the placebo group (Table 2; least-squares [LS] mean: 5.65 vs 6.09 cm/year). The difference in the LS mean GV (TAA-AQ minus placebo) was statistically significant (~0.45 cm/year; 95% CI: -0.78 to -0.11; P = .01). Distributions of GV in the 2 treatment groups were close to normal and similar in shape, except for the shift in mean (Fig 3), indicating that the difference in mean is a good parameter to quantify treatment effect. Growth was not severely affected in any subject in the TAA-AQ group.

The evaluation of the PP population showed similar results. Mean GV was lower in the TAA-AQ group compared with the placebo group during the first 4 months of the double-blind treatment period (LS mean difference: -1.02 cm/year; 95% CI: -1.55 to -0.48; P < .01), and the difference was not statistically significant during months 4–12 (post hoc P = .07). Analyses of the mean height change from baseline and mean GV from visit to visit showed that slower growth occurred in the TAA-AQ group within the first 2 months of the double-blind treatment period (Fig 4). GVs evaluated by age subgroup, gender, and race as well as in various subject populations showed consistent trends in the difference between treatment groups (Fig 5). The difference in GV with age was adjusted in the primary analysis by incorporating the baseline GV and age group as covariates. Additional analysis incorporating the actual value of age as a continuous covariate did not find a significant difference in treatment effect with age.

Table 3 shows the change in GV percentile from baseline. Height SD score was calculated as the number of SDs away from the age-specific median according to the NCHS. A plot of height SD scores at the end of treatment versus baseline did not show a large shift in the score in both treatment groups.

In the follow-up period, the mean GV in the TAA-AQ group (6.59 cm/year) had increased nearly to the magnitude observed during the screening/baseline period (6.70 cm/year), whereas the mean GV in the placebo group had decreased slightly (5.89 cm/year in the follow-up period vs 6.06 cm/year during the screening/baseline period and 6.01 cm/year during the double-blind treatment period).

During the double-blind treatment period, the LS mean reductions from
baseline in daily morning instantaneous TNSS were –2.80 and –2.68 in the TAA-AQ and placebo groups, respectively, and the difference was not statistically significant. Similar results were observed for the individual nasal symptom scores, except for sneezing. For both subject and physician global evaluations of efficacy, the TAA-AQ group showed better mean improvement scores at 12 months (P < .05).

Safety
At the end of treatment, the mean changes from baseline in the 24-hour urinary free cortisol level were –0.01 and –0.31 μg (post hoc P = .69) and in the cortisol/creatinine ratio were –3.77 and –3.27 μg/g creatinine (post hoc P = .78) in the TAA-AQ and placebo groups, respectively (Supplemental Fig 6 A and B). No clinically relevant changes in bone age (Table 4), vital signs, weight, BMI, or physical examinations were observed.

DISCUSSION
In this study, a statistically significant, although clinically nonsignificant, reduction in GV was observed during the 1-year treatment with TAA-AQ (110 μg QD) versus placebo in prepubescent children (aged 3–9 years) with PAR. This difference was evident within the initial 2 months of the double-blind treatment period and most pronounced during the first 4 months. In the follow-up period, the GV approached baseline in the TAA-AQ group, whereas a slight decrease from baseline was noted in the placebo group. Safety evaluations revealed that TAA-AQ was well tolerated, with no evidence of clinically relevant effects on the hypothalamic-pituitary-adrenal (HPA) axis function or bone age. Previous randomized controlled trials assessing GVs of children with PAR treated with INCs have yielded conflicting results. Treatment with fluticasone propionate, budesonide, and mometasone furoate aqueous nasal sprays showed no significant differences in GVs after 1 year of treatment using study designs that did not conform to the FDA guidelines for evaluating effects of INCs on growth of children. In contrast, significantly lower growth rates were observed with beclomethasone dipropionate (BDP) and fluticasone furoate nasal spray (unpublished data conforming to FDA guidelines). These differences might be attributed to the inherent dissimilarities in the pharmacodynamic profiles and bioavailability of the drugs or the heterogeneity in the methods used to assess the pharmacodynamics and level of compliance with the FDA guidelines. Earlier studies (a highly controlled study assessing the lower leg growth by knemometry during the 2-week treatment period and a less well-controlled study assessing the statural growth by stadiometry during the 1- to 2-year treatment

TABLE 2 Summary of GV and Comparison Between Treatment Arms During the Double-Blind Treatment Period: mITT Population

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>TAA-AQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>GV during screening/baseline period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>133</td>
<td>134</td>
</tr>
<tr>
<td>Mean (SD), cm/y</td>
<td>6.06 (3.15)</td>
<td>6.70 (4.09)</td>
</tr>
<tr>
<td>GV during double-blind treatment period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>133</td>
<td>134</td>
</tr>
<tr>
<td>Mean (SD), cm/y</td>
<td>6.01 (1.32)</td>
<td>5.61 (1.56)</td>
</tr>
<tr>
<td>LS mean (SE), cm/y</td>
<td>6.09 (0.122)</td>
<td>5.65 (0.122)</td>
</tr>
<tr>
<td>Difference between treatment arms, LS mean (95% CI), cm/y</td>
<td>—</td>
<td>-0.45 (-0.78 to -0.11)</td>
</tr>
<tr>
<td>P value for difference between treatment arms</td>
<td>—</td>
<td>.01</td>
</tr>
<tr>
<td>GV during follow-up period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>108</td>
<td>111</td>
</tr>
<tr>
<td>Mean (SD), cm/y</td>
<td>5.89 (3.75)</td>
<td>6.59 (4.57)</td>
</tr>
</tbody>
</table>

LS mean, LS mean difference, 95% CI, and P value were calculated by using an analysis of covariance model, with treatment arm, age group (at visit 1), and gender as fixed effects and baseline growth velocity as a covariate.

FIGURE 3
Distribution of growth velocity during treatment period – mITT population.
period\textsuperscript{13} in children with AR did not find a significant effect of TAA-AQ (110 and 220 µg) versus placebo on GV or rate. Typically, a negative result for INC dose in a knemometry study predicts a negative result for the same INC dose in a longer-term stadiometry study.\textsuperscript{21} Unexpectedly, a statistically significant reduction in GV with TAA-AQ relative to placebo during the 12-month treatment period was reported in this study (LS mean: 5.65 vs 6.09 cm/year). These contrasting results may be because our study was designed to reduce the data variability from the following several aspects: prepubertal subjects (3–9 years) usually show a linear growth pattern; height was recorded at multiple visits during the treatment period and multiple measurement readings were taken at each visit to reduce the measurement error; and, most importantly, there was a long study duration, because the variability (SD) of GV is inversely proportional to the length of the time interval of evaluation. The effect size of TAA-AQ in this study was smaller than that in the BDP INC study\textsuperscript{18} (mean change in standing height from baseline at 12 months was 5.0 cm for the BDP-treated patients and 5.9 cm for the placebo-treated patients, \(P < .01\)), and its detection was likely facilitated by the use of FDA-recommended rigorous design elements. The designs in the previous negative TAA-AQ studies may not have been sufficiently sensitive to detect the small effect.\textsuperscript{13,14} INCs seem to exert their effect on growth within a few months of treatment initiation. Evident differences in GVs in the first 4 to 6 weeks of treatment were noted in prepubescent children with PAR treated with intranasal BDP for 1 year\textsuperscript{18} and children with asthma treated with orally inhaled BDP for 30 weeks.\textsuperscript{22} Similarly, in our study, the difference in GVs between TAA-AQ and placebo groups was observed within the first 2 months of treatment, suggesting that the effect of exogenous corticosteroids on growth occurs early and stabilizes during the treatment period. Furthermore, growth suppression with INCs observed in short-term growth studies\textsuperscript{23} suggests that their effect on growth is initial rather than progressive. However, the interpretation of short-term findings in the context of long-term outcomes remains debatable.\textsuperscript{24} Interestingly, these findings raise questions about the safety surrounding recommendations for seasonal versus continuous INC use in children with PAR.

FIGURE 4
Change in (A) height and (B) growth velocity between visits at various time points in mITT population.
Research indicates that the initial effect of steroidal therapy on growth might be reversible in prepubertal children. Results of an open, nonrandomized study in this specific pediatric population treated with inhaled budesonide or fluticasone showed a decrease in height velocity scores in the first 6 to 12 months; these scores returned to baseline after 24 months and were slightly above baseline after 36 months.25 A similar observation of accelerated growth at follow-up was seen in previous asthma studies.26,27 In this study, GV at follow-up reached pretreatment levels in the TAA-AQ group and, in fact, was numerically higher than that in the placebo group. Although earlier studies in children with asthma treated with orally inhaled corticosteroids have reported catch-up growth to reach the normal or near-normal adult height,28–30 a recent 12.5-year follow-up of ∼91% children enrolled in the landmark Childhood Asthma Management Program (CAMP) study found that the height deficit observed at 1 to 2 years after treatment initiation persisted into adulthood; this deficit was neither progressive nor cumulative.29,31 However, substantial differences in the bioavailability of intranasal and orally inhaled corticosteroids in patients with rhinitis and asthma, respectively,8,32 preclude the extrapolation of the results from pediatric asthma studies to patients with PAR.

Consistent with results of a previous study,18 this study detected an effect of INCs on growth in the absence of an effect on the HPA axis function, supporting the position that growth suppression is a more sensitive indicator of systemic bioavailability than HPA axis suppression. The fact that nasally administered TAA-AQ does not suppress HPA axis function at therapeutic dosages has also been observed previously.33 TAA-AQ was well tolerated; the majority of AEs were mild to moderate in intensity. The TEAEs were comparable among treatment groups, similar to those reported in a previous study with TAA-AQ in children with PAR.12 This first published study examining growth effects of INCs in pediatric patients with PAR in compliance with the new FDA guidance detected a small yet statistically significant effect of TAA-AQ on GV with, however, a few limitations. The relatively short follow-up period precludes extrapolations of the rebound growth or effect of pediatric TAA-AQ treatment to the adult height. Minority populations (American Indians and Alaska natives) were not well represented in this study. Moreover, the study could not draw definitive conclusions about the secondary end point, efficacy, because of lack of

### TABLE 3 Change in the GV Percentile From Baseline to Double-Blind Treatment Period According to the 3rd and 97th Percentiles of GV: mITT Population

<table>
<thead>
<tr>
<th>Percentile Status at Baseline</th>
<th>Placebo, n (% of N)</th>
<th>TAA-AQ, n (% of N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>N2</td>
<td>N1</td>
</tr>
<tr>
<td>&lt;3%</td>
<td>20 (5.0)</td>
<td>19 (85.0)</td>
</tr>
<tr>
<td>≥3% to ≤97%</td>
<td>103 (4.9)</td>
<td>98 (85.1)</td>
</tr>
<tr>
<td>&gt;97%</td>
<td>10 (0)</td>
<td>9 (90.0)</td>
</tr>
<tr>
<td>Total</td>
<td>133 (5.8)</td>
<td>126 (94.7)</td>
</tr>
</tbody>
</table>

The denominator (N) is the number of subjects in the specified category of baseline period status. Subjects with missing GV at either baseline or double-blind treatment period were excluded. Note: A weighted average of percentile values provided in the Baumgartner growth chart was used. The P value derived from a Cochran-Mantel-Haenszel test to compare the distributions between the 2 treatment groups, controlling for the percentile status at baseline, was 0.16.
restrictions on the use of rescue and other concomitant medications.

CONCLUSIONS

Using rigorous FDA-recommended study design elements, this study found a small yet statistically significant effect of intranasal TAA-AQ on the GV of children with PAR. However, the GV approached baseline in the TAA-AQ group in the follow-up period, suggesting a possible catch-up growth. Future growth studies of INCs should specifically incorporate the FDA-recommended study design elements and characterize the long-term growth effect more precisely.

ACKNOWLEDGMENTS

We thank all the XRG5029C/3503 study subjects, parents, and clinical investigators and former employees of Sanofi-aventis, Drs George Georges and Yuning Liao, for their contributions to the study design and oversight. Medical writing services were provided by Miss Anupama Singh of Cactus Communications. The study and medical writing services were supported by Sanofi US. The authors retained full control of the manuscript content.

REFERENCES

4. Wallace D, Dykewicz MS, Bernstein DI, et al; Joint Task Force on Practice; American Academy of Allergy, Asthma & Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol. 2008;122(2 suppl):S1–S84
8. US Food and Drug Administration. Guidance for industry—orally inhaled and intranasal corticosteroids:

TABLE 4 Summary of Bone Age at Assessment Visits: Safety Population

<table>
<thead>
<tr>
<th>Bone Age Category at Baseline</th>
<th>Bone Age Category at the End of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>N_i</td>
<td>Placebo, n (% of N_i)</td>
</tr>
<tr>
<td>C-Age – 1</td>
<td>Within C-Age ± 1</td>
</tr>
<tr>
<td>&lt; &lt;C-Age – 1</td>
<td>2</td>
</tr>
<tr>
<td>Within C-Age ± 1</td>
<td>100</td>
</tr>
<tr>
<td>&gt;C-Age + 1</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>105</td>
</tr>
</tbody>
</table>

The denominator (N_i) is the number of subjects in the specified category of baseline period status. Subjects with missing bone age data at either baseline or the end of treatment were excluded. Note: The P value derived from a Cochran-Mantel-Haenszel test to compare the distributions between the 2 treatment groups, controlling for the bone age category at baseline, was 0.41. C-age, chronological age.


Intranasal Triamcinolone and Growth Velocity
David P. Skoner, William E. Berger, Sandra M. Gawchik, Akbar Akbary and Chunfu Qiu

*Pediatrics* 2015;135:e348; originally published online January 26, 2015;
DOI: 10.1542/peds.2014-1641

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/135/2/e348.full.html