Inhaled Fluticasone Propionate by Diskus in the Treatment of Asthma*

A Comparison of the Efficacy of the Same Nominal Dose Given Either Once or Twice a Day

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Study objective: In September 2000, the US Food and Drug Administration (FDA) approved the use of Flovent Diskus (FD) [fluticasone propionate; GlaxoSmithKline; Research Triangle Park, NC], which is an orally inhaled, dry-powder corticosteroid, for the maintenance treatment of asthma at dosages of 50 to 1,000 μg administered twice-daily. Once-daily dosage regimens did not receive approval. This article will detail six clinical trials, five of which incorporated comparative once-daily and twice-daily treatment arms of the same nominal dose of FD.

Design: Six 12-week, randomized, double-blind, placebo-controlled studies in patients with mild-to-moderate asthma, including two pediatric asthma trials (patient age, 4 to 11 years) of total daily doses of fluticasone propionate (FP) of 100 or 200 μg, and four adult and adolescent studies of total daily doses of FP of 100, 200, or 500 μg.

Results: Twice-daily dosing was numerically superior to once-daily dosing at the same nominal dose in all comparative studies for the primary end point, change in predose FEV1. In five trials, the results of the once-daily dosage of FP were statistically indistinguishable from those with placebo. One trial demonstrated the superiority of FP, 500 μg once-daily, over placebo; however, the effect size was half that observed with twice-daily dosing. Once-daily FP dosing showed no advantage in safety or in patient adherence to medication.

Conclusions: In the FDA review of once-daily dosing of the FD regimen, 100 or 200 μg once-daily dosing was not shown to be significantly better than placebo. FP 500 μg once-daily was found to be superior to placebo, but at about one half the effect size as the same nominal dose given bid. No advantage in patient safety or adherence was demonstrated for once-daily administration over twice-daily administration, and once-daily administration is not currently recommended.

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Key words: asthma; Diskus; dose regimen; Flovent; fluticasone propionate; multidose powder inhaler; pediatric study

Abbreviations: AUC = area under the curve; BDP = beclomethasone dipropionate; BDT = bronchodilator therapy; FD = Flovent Diskus; FP = fluticasone propionate; ICS = inhaled corticosteroid; PEFR = peak expiratory flow rate

Flovent Diskus (FD) is a dry-powder formulation of fluticasone propionate (FP), which was approved in September 2000 for the maintenance treatment of asthma for patients aged ≥ 4 years as twice-daily therapy. Just prior to approval, two articles appeared in CHEST1,2 that detailed administration of the same nominal dose of FD as once-daily therapy instead of divided twice-daily therapy. The first article1 was a dose-ranging study of FD admin-
istered once daily, and it concluded that FD “showed dose-related improvements in some efficacy parameters” that “confirm the high therapeutic potential of fluticasone propionate.” The second article was a placebo-controlled, comparative study of once-daily or twice-daily FD administered to patients with moderate asthma. That article concluded that “once-daily dosing with fluticasone propionate may be an option for patients with mild-to-moderate asthma.” A third article has since been published that concluded that FP, 250 µg once daily, is “an additional therapeutic option.” Such assertions should be informed by the “totality” of the data.

The original new drug application package consisted of nine randomized clinical trials, five of which contained comparisons of twice-daily dosing to once-daily dosing, and one of which was considered to be a once-daily “dose-ranging” study. Three of the five comparative studies included adult and adolescent subjects aged ≥ 12 years who were receiving FP in total daily doses of 200 to 500 µg. One of these studies randomized inhaled corticosteroid (ICS)-naïve subjects and one randomized ICS-using subjects. The third study included both ICS-naïve and ICS-using subjects. The remaining two investigations studied pediatric subjects (age range, 4 to 11 years) who had been treated with total daily doses of FP of 100 or 200 µg.

This article will summarize the results of the dose-ranging study (FLTA2016) and the five safety and efficacy trials, including the one previously published (FLTA2005), in order to provide a comprehensive review of the clinical data presented in the FD new drug application and to give practitioners more information on the use of once-daily or twice-daily FD therapy.

**General Features of Clinical Trial Design**

All trials were 12-week, randomized, double-blind, placebo-controlled, double-dummy, parallel-group studies of FD. All patients were issued an albuterol inhaler to use as a rescue bronchodilator. Strict discontinuation criteria for asthma instability based on lung function were followed. Studies FLTA2003 and FLTA2004 also included active comparator beclomethasone dipropionate (BDP), 168 µg bid.

The primary population for analysis was the intent-to-treat, and all statistical tests were two-sided with differences of ≤ 0.05 considered to be significant. Pairwise comparisons were performed without adjusting individual p values; however, stepwise comparisons could proceed only if the overall test (ie, group F test) among treatment groups was statistically significant compared to placebo. The primary efficacy variable was the morning predose FEV₁, and for pediatric studies, the morning predose peak expiratory flow rate (PEFR) was added as a coprimary end point, allowing the inclusion of data from children who were unable to perform an adequate FEV₁ maneuver (see the “Pediatric Studies” section). Secondary efficacy variables included survival-in-study, physician global assessment, patient-recorded morning and evening PEFR, symptom scores, rescue bronchodilator use, and nighttime awakenings requiring bronchodilator therapy (BDT). The primary health-related quality-of-life outcome or patient-reported outcome instrument was the asthma quality-of-life questionnaire of Juniper et al.

A brief summary of each individual trial is presented below.

**Adolescent/Adult Studies**

**Study FLTA2003**

This study compared FD, FP (100 µg bid and 200 µg qd), BDP (168 µg bid), and placebo in ICS-using asthmatic patients aged ≥ 12 years of either gender who reported ≥ 6 months of American Thoracic Society-defined mild-to-moderate persistent asthma. Spirometry criteria included best value for FEV₁ at 50 to 80% of predicted. The use of ICSs for at least 3 months before study entry was required, and for at least 2 weeks of this time the dose of BDP or triamcinolone acetonide was to be at 5 puffs per day.

All data from subjects discontinued prior to study end were included in the analysis as a last-value-carried-forward to the end point to avoid possible bias introduced by the dropout of “sicker” patients, especially among the subjects who received placebo. Enrollment power was planned to provide > 80% power of detecting a difference in FEV₁ of 0.25 L between any two treatment groups.

**Study FLTA2004**

This study compared FP (100 µg bid and 200 µg qd), BDP (168 µg), and placebo in adolescent and adult patients with mild-to-moderate persistent asthma. Clinical trials FLTA2003 and FLTA2004 ran concurrently and were of identical design, differing only in subjects’ baseline ICS usage. FLTA2004 was limited to subjects receiving only BDT at the time of enrollment (ie, ICS-naïve).
Study FLTA2005

This study was reported previously and compared adolescent and adult patients with mild-to-moderate asthma who had been randomized to placebo, FP (250 μg bid), and FP (500 μg qd). Study design and inclusion criteria were similar to those of the previous adult studies, except that both ICS-naïve and ICS-using subjects were included and were stratified by baseline asthma therapy. An open-label extension of 12 months duration was added via amendment to fulfill regulatory requirements to collect adequate safety data. All subjects who chose to continue were switched to active treatment at the start of the extension. No adjustments were made to the statistical plan or power calculations to accommodate an efficacy analysis using a numerically reduced population without a placebo control.

FLTA2016

This study was a dose-ranging trial that compared once-daily administration of FD at doses of 100, 200, and 500 μg to placebo in adult and adolescent subjects aged 12 years with mild-to-moderate persistent asthma. No comparative FP twice-daily treatment arms were included. This study has been reported previously.

The patient population included 330 asthmatic subjects with best mean morning FEV1 values between 45% and 75% of predicted. Subjects were stratified by baseline ICS use (about 55%) or inhaled BDT alone (45%). The protocol-specified statistical analysis included a plan to address the multiple comparisons inherent in a dose-ranging study. Specifically, an overall treatment test (i.e., F test) would be performed first, and if the overall treatment effect did not show statistical significance, the pairwise comparisons would be viewed as descriptive only rather than inferential. Secondary efficacy end points included survival-in-study, morning/evening PEFRs, rescue bronchodilator use, symptom scores, and nighttime awakenings.

PEDiATRIC STUDIES

Study FLTA2007

This study compared the FD (total daily dose, 100 μg), FP (50 μg bid), or FP (100 μg qd) to placebo among asthmatic children aged 4 to 11 years who had persistent asthma. To assess efficacy, the two pediatric studies included both the change from baseline in predose FEV1, as in the adult studies, and the change from baseline in morning predose PEFR, which was formally measured at a pulmonary function testing laboratory at each clinic visit.

Inclusion/exclusion criteria of importance included persistent asthma (as defined by American Thoracic Society criteria), prepubertal status, use of asthma-specific pharmacotherapy of a duration of ≥ 3 months prior to enrollment, stable asthma per protocol definition with no history of life-threatening asthma, no use of nonsteroidal immunosuppressive therapy (including cyclosporin, methotrexate, or gold), and no significant concomitant disease.

Study FLTA2008

This study was of identical design to FLTA2007 except that it compared FD (total daily dose, 200 μg), FP (100 μg bid), or FP (200 μg qd) to placebo among asthmatic children aged 4 to 11 years with persistent asthma. The study was later amended to permit open-label use of FP during a 12-month extension, again to collect safety data to meet regulatory requirements for a new drug product in a pediatric population. Subjects were stratified at baseline for the use of ICSs or inhaled cromolyn, or the use of BDT alone.

RESULTS

Tables 1-4 and Figure 1 summarize the results of the primary and secondary efficacy variable for all studies.

Study FLTA2003

Two hundred ninety-nine subjects completed the screening period, were randomized, and were entered into the double-blind treatment phase of the trial (placebo, 73 subjects; FP [100 μg bid], 73 subjects; FP [200 μg qd], 77 subjects; and BDP [168 μg bid], 76 subjects). Eighty-four of these subjects (28%) discontinued prior to study end point (placebo group, 48%; FP, 100 μg bid, group, 22%; FP, 200 μg qd, group, 17%; and BDP, 168 μg bid, group, 26%). The most common reason for discontinuation (49%) was lack of efficacy by predefined criteria (14% overall), with 20 subjects (26%) from the BDP, 168 μg bid, group, 13 subjects (17%) from the FP, 200 μg qd, group, 16 subjects (22%) from the FP, 100 μg bid, group, and 35 subjects (48%) from the placebo group.

Primary Efficacy Variable: At the end point, there was a statistically significant overall treatment effect (p = 0.001 [F test]) allowing for pairwise comparisons. Pairwise comparisons between placebo and each of the three treatment groups showed statistical significance for both the BDP and the FP twice-daily regimens, but not for the FP once-daily regimen. The mean change from baseline in FEV1
for active treatment arms (Table 1) vs placebo was 0.28 L for FP (100 μg bid), 0.27 L for BDP (168 μg bid), and 0.16 L for FP (200 μg qd). It is worth pointing out that both twice-daily regimens achieved the prespecified effect size of 0.25 L that the study was powered to detect, but the FP once-daily treatment arm did not. The pairwise comparison between BDP and once-daily FP therapy showed the difference to be significant (p = 0.048), although not between the FP once-daily regimen and the FP twice-daily regimen (p = 0.112).

Secondary efficacy variables revealed findings similar to the primary efficacy variable and are summarized in Table 3.
Study FLTA2004

Two hundred seventy-one subjects were randomized into the trial. One hundred fifty-two subjects (56%) completed the trial with 78 subjects (29%) withdrawing from the study due to lack of efficacy, with 33 subjects (48%) withdrawing from the placebo group, 12 subjects (18%) withdrawing from the FP, 100 μg bid, group, 21 subjects (45%) withdrawing from the FP, 200 μg qd, group, and 24 subjects (17%) withdrawing from the BDP, 168 μg bid, group. Subjects enrolled in FLTA2004 generally had more severe asthma than did subjects in FLTA2003, as determined by the use of ICSs at baseline.

Primary Efficacy Variable: At the end point, there was a statistically significant group treatment effect overall (p = 0.002 [F test]). Pairwise comparisons between placebo and each of the three treat-
ment groups showed statistical significance for both the FP and BDP twice-daily regimens (p = 0.002). FP once-daily therapy was not statistically significant compared to placebo (p = 0.055). The mean change from baseline in FEV₁ demonstrated an effect size of 0.35 L for the FP, 100 µg bid, group, 0.33 L for the BDP, 168 µg bid, group, and 0.19 L for the FP, 200 µg qd, group vs the placebo group. The pairwise comparison between the once-daily and twice-daily FP regimens trended toward significance, but was not significant (p = 0.079).

By study end, 33 subjects (48%) in the placebo group had discontinued participation for lack of efficacy compared to 12 subjects (18%) in the FP, 100 µg bid, group, 21 subjects (32%) in the FP, 200 µg qd, group, and 12 subjects (17%) in the BDP group.

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**Table 3—Results of Secondary Efficacy Variable For Adult and Adolescent Studies***

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>FP qd</th>
<th>FP bid</th>
<th>BDP bid</th>
<th>Overall p Value</th>
</tr>
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<tbody>
<tr>
<td>FLTA2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaplan-Meier discontinuation Lack of efficacy, No. (%)</td>
<td>19 (26)</td>
<td>7 (9)</td>
<td>5 (7)</td>
<td>10 (13)</td>
<td>0.005</td>
</tr>
<tr>
<td>p value vs placebo</td>
<td>0.008</td>
<td>0.007</td>
<td>NS</td>
<td>0.005</td>
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</tr>
<tr>
<td>AM PEFR Change from baseline (L/min)</td>
<td>1</td>
<td>31</td>
<td>27</td>
<td>31</td>
<td>0.002</td>
</tr>
<tr>
<td>p value vs placebo</td>
<td>&lt; 0.001</td>
<td>0.005</td>
<td>&lt; 0.001</td>
<td>0.001</td>
<td></td>
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<tr>
<td>Asthma symptom scores Change from baseline</td>
<td>−0.12</td>
<td>−0.37</td>
<td>−0.40</td>
<td>−0.38</td>
<td></td>
</tr>
<tr>
<td>p value vs placebo</td>
<td>0.063</td>
<td>0.016</td>
<td>0.013</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Nighttime awakenings Change from baseline</td>
<td>−0.03</td>
<td>−0.06</td>
<td>−0.06</td>
<td>−0.06</td>
<td></td>
</tr>
<tr>
<td>p value vs placebo</td>
<td>0.065</td>
<td>0.3</td>
<td>0.112</td>
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<tr>
<td>Albuterol requirement Change from baseline</td>
<td>0.22</td>
<td>−0.82</td>
<td>−1.07</td>
<td>−0.90</td>
<td>0.002</td>
</tr>
<tr>
<td>p value vs placebo</td>
<td>0.019</td>
<td>0.004</td>
<td>&lt; 0.001</td>
<td>0.002</td>
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</tr>
<tr>
<td>FLTA2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaplan-Meier discontinuation Lack of efficacy, No. (%)</td>
<td>33 (48)</td>
<td>21 (32)</td>
<td>12 (18)</td>
<td>12 (17)</td>
<td>0.001</td>
</tr>
<tr>
<td>p value vs placebo</td>
<td>0.045</td>
<td>0.001</td>
<td>0.001</td>
<td></td>
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</tr>
<tr>
<td>Morning PEFR Change from baseline, L/min</td>
<td>−12</td>
<td>−3</td>
<td>18</td>
<td>13</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>p value vs placebo</td>
<td>0.153</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
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<tr>
<td>Asthma symptom scores Change from baseline</td>
<td>0.14</td>
<td>−0.03</td>
<td>−0.23</td>
<td>−0.17</td>
<td>0.003</td>
</tr>
<tr>
<td>p value vs placebo</td>
<td>0.035</td>
<td>0.001</td>
<td>0.011</td>
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<tr>
<td>Nighttime awakenings Change from baseline</td>
<td>0.07</td>
<td>−0.01</td>
<td>−0.01</td>
<td>−0.03</td>
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<tr>
<td>p value vs placebo</td>
<td>0.156</td>
<td>0.318</td>
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<tr>
<td>Albuterol requirement Change from baseline</td>
<td>1.29</td>
<td>−0.11</td>
<td>−0.43</td>
<td>−0.37</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>p value vs placebo</td>
<td>0.003</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
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<tr>
<td>FLTA2005</td>
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<td></td>
</tr>
<tr>
<td>Kaplan-Meier discontinuation Lack of efficacy, No. (%)</td>
<td>45 (54)</td>
<td>21 (25)</td>
<td>7 (8)</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>p value vs placebo</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
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</tr>
<tr>
<td>p value FP bid vs FP qd</td>
<td></td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morning PEFR Change from baseline (L/min)</td>
<td>−15</td>
<td>32</td>
<td>35</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>p value vs placebo</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma symptom scores Change from baseline</td>
<td>0.16</td>
<td>−0.32</td>
<td>0.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p value vs placebo</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
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<tr>
<td>Nighttime awakenings Change from baseline</td>
<td>0.09</td>
<td>−0.01</td>
<td>−0.03</td>
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<tr>
<td>p value vs placebo</td>
<td>0.012</td>
<td>0.048</td>
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<tr>
<td>Albuterol requirement Change from baseline</td>
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<td>−0.67</td>
<td>−1.05</td>
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<tr>
<td>p value vs placebo</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
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<tr>
<td>p value FP bid vs FP qd</td>
<td></td>
<td>0.030</td>
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</table>

*NS = not significant.
A total of 253 subjects were enrolled into the study.2 There were 95 withdrawals, with lack of efficacy accounting for 73 withdrawals (29%), with 45 withdrawals (54%) from the placebo group, 7 withdrawals (8%) from the FP, 250 μg bid, group, and 21 withdrawals (25%) from the FP, 500 μg qd, group.

Primary Efficacy Variable: At the end point, there was a statistically significant overall group result on the F test (p < 0.001) and individual improvement in FEV1 in each FP treatment group, with an effect size of 0.57 L for the twice-daily group and 0.29 L for the once-daily group vs placebo. The numerical difference in FEV1 between once-daily and twice-daily therapy was substantial, and the pairwise comparison between the two active treatment arms was statistically significant (p < 0.001).

At the end of the study, 45 subjects (54%) in the placebo group had discontinued participation for lack of efficacy compared to 7 subjects (8%) in the FP, 250 μg bid, group and 21 subjects (25%) in the FP, 500 μg qd, group. Although not powered to detect treatment differences between active agents for this end point, there was a significant difference in survival-in-study between the two FP arms (p = 0.001) favoring twice-daily therapy.

Study FLTA2007

There were 262 children receiving at least one dose of study medication, with 169 completing the study, for an overall dropout rate of 35%. Most children withdrew due to lack of efficacy (most commonly because their PEFR fell below stability limits) with a 26% overall withdrawal rate (placebo group, 29 withdrawals [35%]; FP, 50 μg bid, group, 17 withdrawals [19%]; FP, 100 μg qd, group, 23 [25%]).

Primary Efficacy Variable FEV1: At the end point, the overall group treatment effect was not statistically significant. This was true whether the difference was expressed as "liters" or as "% change
from baseline” or as “change from baseline in %-predicted.” Numerically, the largest mean change was shown by the FP (50 μg bid) group (0.13 L) followed by the FP (100 μg qd) group (0.08 L), then by placebo (0.05 L). Although pairwise comparisons should be considered exploratory in the absence of an overall treatment effect, it is worth noting that such comparisons demonstrated no significant difference between placebo and either the FP (100 μg qd) or FP (50 μg bid) regimens. When examined on a week-by-week basis, the pairwise comparison of change from baseline in FEV1 did not achieve statistical significance for FP once-daily therapy for any week assessed during this 12-week study, although the FP twice-daily regimen did show efficacy on some but not all weekly assessments.

While FLTA2007 might be considered a “failed study” because of its inability to separate active treatment from placebo based on the FEV1 values, some information may be inferred from the results shown by the co-primary end point, clinic morning PEFR.

**Primary Efficacy Variable PEFR:** The co-primary efficacy end point in this trial was the mean change from baseline in morning PEFR. There was no statistically significant overall group treatment effect for the end point clinic morning PEFR. Exploratory pairwise comparisons demonstrated that, numerically, the FP (50 μg bid) treatment arm achieved an “effect size” (ie, 27.8 L/min) nearly double that of the FP (100 μg qd) treatment group (ie, 15.3 L/min), and that this difference for FP twice-daily therapy vs placebo reached a level of significance (p = 0.038), while FP once-daily therapy was not significant in comparison to placebo. Secondary efficacy variables are summarized in Table 4. Significant survival-in-trial comparisons were noted only for twice-daily therapy group (p = 0.014) and not for the once-daily therapy group (p = 0.095) when compared to the placebo group.

**Study FLTA2008**

There were 242 children receiving at least one dose of study medication, with 142 completing the study, for an overall dropout rate of 41%. These children were receiving ICS therapy at baseline and generally had more severe asthma than the patients in study FLTA2007.

Most children withdrew from the study for lack of efficacy (83 children; most commonly withdrew because their PEFR fell below stability limits) with a 34% overall withdrawal rate (placebo group, 42 subjects [54%]; FP, 100 μg bid, group, 16 subjects [20%]; FP, 200 μg qd, group, 25 subjects [30%]).

**Co-Primary Efficacy Variable FEV1:** At the end point, there was a statistically significant overall
treatment effect in FEV$_1$ (p < 0.001 [F test]) in the mean change from baseline. In pairwise comparisons with placebo, there was a significant difference in the mean change from baseline in FEV$_1$ for each of the two FP groups (p < 0.001) without a significant difference between the two FP arms. The treatment effect was 0.27 L for twice-daily treatment compared to 0.16 L for once-daily therapy.

Co-Primary Efficacy Variable PEFR: Clinic morning PEFR showed no significant overall group treatment effect, and pairwise comparisons between placebo and twice-daily or once-daily FP therapy therefore should be considered to be exploratory. When measured as the mean change or the change in percent predicted, the twice-daily treatment group reached a significant level (p = 0.002 and p = 0.007, respectively) compared to placebo. However, using the same exploratory once-daily dosing was not significant in the pairwise comparison with placebo.

The absence of an overall treatment effect using the parameter PEFR is an important observation, given that the performance of an adequate PEFR was considered less age-dependent than performance of an adequate FEV$_1$. It was assumed that PEFR could be performed by all children enrolled in the trial, including those who were 4 and 5 years old. In many respects, PEFR may measure the overall efficacy of therapy more comprehensively in the pediatric population recruited for this trial.

Secondary efficacy variables are summarized in Table 4 and exhibit the same trends as the primary efficacy variables.

Safety

Safety data for the drug substance FP by the inhalation route is extensive, and a detailed review is beyond the scope of this article. Unfortunately, the comparative safety data essential to support a once-daily dosing schedule for this product were not provided by these trials. At a minimum, such an assessment should encompass the relative impact of the two dosing schedules on known systemic corticosteroid adverse effects. Relevant parameters might include growth velocity in children, bone density or fracture incidence in adults, and impact on the hypothalamic-pituitary-adrenal axis in subjects of all ages.

Unpublished pharmacokinetic data (from the US Food and Drug Administration) support the assertion that comparable systemic exposure, as measured by FP area under the curve (AUC) concentrations, may be achieved whether the same nominal dose of FP is administered once-daily or is divided into twice-daily treatment. For this reason, it should not be assumed that systemic safety will be improved with once-daily dosing. To the contrary, depending on whether corticosteroid-related adverse events correlate with exposure (i.e., FP AUC) or FP peak serum concentrations, a safety disadvantage may actually exist.

The above studies demonstrate that efficacy is lost when FP given at the same nominal dosing is changed from twice-daily to once-daily administration. In order to maintain the same risk/benefit ratio, data showing a true safety advantage for once-daily administration should be demonstrated.

Discussion

This article has summarized what is known regarding the absolute and relative efficacy of once-daily and twice-daily FD therapy compared to placebo, both for 12-week trials and in the longer term. As noted in the introduction, there are published reports advocating the use of once-daily FD therapy. This review of studies, however, reveals that once-daily dosing of FP given at doses of ≤ 200 μg failed to demonstrate efficacy in six trials. Once-daily dosing of FP, 100 μg qd, failed to demonstrate efficacy on the primary end point in one pediatric study (FLTA2007) and one adult study (FLTA2106). Similarly, FP, 200 μg qd, failed to demonstrate efficacy on the primary end point for three adult trials (FLTA2003, FLTA2004, and FLTA2016) and one pediatric trial (FLTA2008). The maximum of the three doses of FP that were tested (500 μg qd) demonstrated a statistically significant difference compared to placebo in the primary end point (change in FEV$_1$) in a single clinical trial (FLTA2005). However, as in all the other studies, once-a-day dosing was numerically and statistically inferior to the FP, 250 μg bid, regimen. The secondary end points for all these studies supported the conclusion reached by the primary end point analysis favoring the efficacy for the twice-daily dosing schedule, while failing to provide convincing support for once-daily dosing of FD (Table 3), and in particular the secondary assessment, in-study survival (a measure of asthma control), favored twice-daily therapy over once-daily therapy.

As previously reported, FLTA2016 was a dose-ranging study of once-daily FD that employed a different statistical analysis in the published version of the trial than was presented to the US Food and Drug Administration. Specifically, FLTA2016 failed to show an overall group treatment effect of FP vs placebo on the primary end point, and it was therefore inappropriate to perform the pairwise analysis.
that led to the statistical significance of therapy with FP (500 μg qd) compared to placebo without clarifying the exploratory nature of that comparison. It is clear that administering the drug once a day is inferior to the same nominal dose divided and administered twice a day and that similar efficacy for a once-daily dosing regimen obtained by increasing the dose above the twice-daily dosing level will result in increased local and systemic exposure to FP and the known risks of corticosteroid use.9–11

If inferior efficacy is to be accepted as a tradeoff for patient convenience or compliance, then at the very least the once-daily regimen should pose no greater safety risk. Indeed, from a true risk/benefit perspective, the regimen should provide some safety advantage in exchange for reduced efficacy. No evidence in support of a safety advantage was provided by these trials. Indeed, data exist that support the notion that once-a-day same nominal dosing compared to twice-daily dosing may result in a safety disadvantage.12 This makes sense as higher peak serum concentrations may conceivably surpass some critical "adverse event" threshold, while maintaining an AUC similar to that achieved with 12-h dosing.

For study FLTA2005, which was a 12-week comparison of once-daily to twice-daily FD, followed by a 1-year open-label extension conducted to acquire additional safety information, ZuWallack et al concluded that "reducing the frequency of dosing over a long-term period of 1-year did not result in deterioration in lung function." However, the data from the open-label extension have been inappropriately used to support these conclusions, as the open-label extension of study FLTA2005 was conducted to meet the regulatory requirements for adequate safety information for licensing a new drug product and was not designed or powered to obtain comparative efficacy information. The conclusion that there was no difference in asthma control between the two active treatment arms would have required that an equivalency or a noninferiority study be conducted. The subject numbers of this extension were inadequate for a noninferiority study to provide sufficient power to detect a difference in asthma control between the two active treatments. Also, due to the open-label design of the study the results would be confounded by selection bias, given that subjects voluntarily chose to continue beyond the initial 12 weeks of the study. Finally, since this was not a noninferiority study and the open-label extension lacked a placebo control, neither assay sensitivity nor effect sizes can be assured, invalidating any efficacy evaluations.13,14

In summary, for all comparative trials of FD, twice-daily therapy was consistently more effective than the same dose given once-daily. In the presented studies, there was not a demonstrated safety advantage of once-daily therapy compared to twice-daily therapy. Although convenience of drug administration and reduced frequency of dosing may improve patient compliance,15 this reason alone should not be used to advocate a clearly inferior dosing regimen, particularly if there are no other clinical data to suggest a net benefit to the patient.

References

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