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A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of SLI381 (Adderall XR) in Children With Attention-Deficit/Hyperactivity Disorder

Joseph Biederman, MD*; Frank A. Lopez, MD‡; Samuel W. Boellner, MD§; and Mark C. Chandler, MD||

ABSTRACT. Objective. SLI381 (Adderall XR) is a 2-component extended-release capsule formulation of Adderall designed to produce a therapeutic effect that lasts throughout the day with 1 morning dose. The primary objective of this study was to assess the efficacy and safety of SLI381 compared with placebo in the treatment of attention-deficit/hyperactivity disorder (ADHD) in children in a naturalistic school and home setting. A secondary objective was to assess the diurnal variation in responses based on morning and afternoon assessments.

Methods. A multicenter, randomized, double-blind, parallel-group, placebo-controlled trial was conducted at 47 sites. After a 1-week washout of any previous stimulant medication, patients were randomized to receive single-daily morning doses of placebo or SLI381 10 mg, 20 mg, or 30 mg for 3 weeks. Participants aged 6 to 12 years inclusive who satisfied Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria diagnosis of ADHD were included. The primary efficacy parameter was the Conners Global Index Scale for Teachers. Secondary efficacy parameters included the Conners Global Index Scale for Parents, the Clinical Global Impressions Scale for improvement, and the Parent Global Assessment Scale for improvement. Safety was assessed by recording adverse events, laboratory tests, and vital signs at each visit during the study. Physical examinations and electrocardiograms were performed at the screening and the end of the study.

Results. Five hundred eighty-four children were randomized, 563 were included in the intent-to-treat population, and 509 completed the entire study. Intention-to-treat analysis of Conners Global Index Scale for Teachers and Conners Global Index Scale for Parents scores revealed significant improvement in morning, afternoon, and late afternoon behavior for all active treatment groups versus placebo. All active treatment groups showed significant dose-related improvement in behavior from baseline. Both the Clinical Global Impressions Scale for improvement and Parent Global Assessment for improvement showed all doses of SLI381 to be superior to placebo at treatment end and both confirmed the dose-response relationship between improvement and the SLI381 dose. The incidence of spontaneously reported adverse events was low and similar for active treatments and placebo.

Conclusions. SLI381 produced consistent, dose-related improvements on all measures of efficacy. The extended-release nature of the SLI381 formulation was shown by continued, significant improvement in afternoon assessments by teachers and afternoon and late afternoon assessments by parents. The time course and therapeutic effects of SLI381 suggests that this medication is an efficacious once-daily treatment for children with ADHD. Pediatrics 2002;110:258–266; attention-deficit/hyperactivity disorder, amphetamine, Adderall XR, randomized, controlled trial.

ABBREVIATIONS. ADHD, attention-deficit/hyperactivity disorder; ECG, electrocardiogram; DISC, Diagnostic Interview Schedule for Children; CGIS-T, Conners Global Index Scale for Teachers; CGIS-P, Conners Global Index Scale for Parents; CGI, Clinical Global Impressions Scale for improvement; PGA, Parent Global Assessment for Improvement; ITT, intention-to-treat; ANCOVA, analysis of covariance.

Attention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioral disorder affecting from 4% to 12% of school-aged children. This disorder is characterized by developmentally inappropriate levels of inattention, hyperactivity, and impulsivity, and is associated with significant impairment across multiple domains of functioning, including academic and occupational achievement, family and peer relationships, and low self-esteem.

Numerous randomized, controlled trials have shown stimulant medications to be highly effective in ameliorating the symptoms of ADHD. However, their use can be problematic because of the need for multiple daily dosing in most individuals. In-school dosing in pediatric patients may lead to ridicule by peers and further negative impact on self-esteem, compliance, and treatment satisfaction. In addition, many patients may require medication coverage that extends into homework time and organized recreational activities. This denotes a compelling need for more effective once-daily dosage forms of stimulant medications that last throughout the school day and into the evening.

Adderall (Shire US Inc, Valley Stream, NY), a single-entity amphetamine drug product consisting of a mixture of neutral salts of dextroamphetamine sulfate, amphetamine sulfate, the dextro isomer of amphetamine saccharate, and d,l-amphetamine aspar-
tate, is effective in treating the symptoms of ADHD. To address the need for a once-daily dosing option for more patients, a 2-component extended-release formulation (SLI381 capsules [Catalytica Pharmaceuticals, Inc, Greenville, NC]) of Adderall has been developed that is designed to produce pulsed-release of amphetamine salts yielding a therapeutic effect that lasts throughout the day and into the evening with 1 morning dose.

The SLI381 capsule formulation is composed of 2 types of Microtrol beads combined in a 50:50 ratio within 1 capsule. The immediate release beads are designed to release drug content in a time course similar to Adderall. The delayed release beads are designed to release drug content 4 to 6 hours after oral administration of the capsule. With the inclusion of the delayed-release component, the 2-unit formulation, given once a day, is expected to produce similar pharmacokinetic and pharmacodynamic effects as immediate release Adderall given twice daily.

A pilot study compared the bioavailability of 3 composite 20-mg experimental extended release formulations with a single-dose administration against the reference, Adderall 10 mg bid with a 4-hour interval. The selected SLI381 formulation was bioequivalent to Adderall in terms of the d- and l-amphetamine extent and rate of absorption, and the time to maximum concentration values for d- and l-amphetamine were not different from those observed for Adderall bid with a 4-hour interval.

This multicenter study was designed to assess the safety and efficacy of SLI381 in a naturalistic school and home setting. This naturalistic environment allows efficacy and safety results to be extrapolated to the clinical pediatric population most likely to receive stimulant treatment for ADHD. A randomized, double-blind, parallel group design with up to 3 weeks of exposure permits between-group differences in clinical manifestations of childhood ADHD and in acute safety and tolerability to be evaluated.

The primary objective of this study was to assess the efficacy and safety of SLI381 compared with placebo in the treatment of ADHD in children. The secondary objective was to assess diurnal variation in responses to SLI381 based on morning and afternoon assessments. This study was conducted in compliance with institutional review board and informed consent regulations.

METHODS

Participants

Children aged 6 to 12 years who satisfied Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria, and in acute safety and tolerability to be evaluated.

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per week on either Saturday or Sunday. They rated the child 3 times during the day (at 10:00 AM, 1:00 PM, and after 4:00 PM). Parents were also given a diary to record observations of their child’s behavior during the week to aid in completing the Parent’s Global Assessment, which was completed at baseline (washout week) and the final visit. Adverse event information was recorded, and drug compliance was assessed by capsule counts at each weekly study visit.

The primary efficacy parameter was the average of morning and afternoon CGI-S-T total scores at study endpoint (or last treatment week). This included a total of up to 6 assessments, 3 for morning and 3 for afternoon. In addition, the averages of the CGI-S-T scores were calculated separately for both morning and afternoon assessments to evaluate the drug effect versus placebo for morning and afternoon separately.

Secondary efficacy parameters included CGI-P and 2 global assessments of overall improvement by the investigator (the Clinical Global Impressions Scale for improvement [CGI]), and by parents (the Parent Global Assessment for improvement [PGA]). Average total scores were calculated separately for morning, afternoon, and late afternoon CGI-S-T only the improvement score of the CGI and PGA were examined in the study.

Adverse events were recorded by COSTART term and rated as mild, moderate, or severe. Compliance was measured by capsule counts at the end of each visit.

Statistical Analysis

To detect a standardized treatment difference of 0.47 between a single SLI381 treatment group and the placebo group at 90% power (2-tailed) and an α level of 0.05, it was necessary to enroll at least 120 participants in the placebo group and 80 participants in each of the 3 treatment groups (10, 20, and 30 mg/d). Assuming a 20% attrition rate over the course of the study, a total of 450 participants were targeted for inclusion in the study.

The primary efficacy analysis was conducted using the intention-to-treat (ITT) population and a 2-way analysis of covariance (ANCOVA) model with a general linear approach. This ANCOVA model used the average of CGI-S-T total scores over the last treatment week assessed (ie, study endpoint), as the dependent variable, and the treatment (four levels) and study site as the independent variable. The corresponding baseline score (obtained during the single-blind washout week) of the primary endpoint was included as a covariate in the statistical model. SAS PROC GLM (Windows version 6.12) was used for this analysis. If statistically significant treatment effect was disclosed (P < .05), by the 2-way ANCOVA, Dunnett’s test for multiple mean comparisons was used to compare the differences between treatment groups and the placebo group.

A similar analytic approach to the CGI-S-T total scores was adopted for each individual treatment week and for secondary efficacy measures and subgroup population comparisons. For the CGI-S-T, those assessments conducted before noon, exclusive, were operationally categorized as morning assessments; those assessments that were conducted after noon, inclusive, were operationally categorized as afternoon assessments. Similarly, for the CGI-P, morning assessments were those conducted before noon, afternoon assessments were those conducted from noon to 4:00 PM, and late afternoon assessments were operationally categorized as those conducted on or after 4:00 PM. Because participants assigned to SLI381 20 mg and 30 mg received their doses in a dose escalation fashion, a 3-way analysis of variance with split-plot design was used to analyze weekly averages of the CGI-S-T total scores without data imputation for participants who completed the study to evaluate the dose titration effect. Safety-related information was analyzed comparatively for active versus placebo groups, using 1-way analysis of variance, to examine differences in changes from baseline to end of study.

RESULTS

Study Population

Six hundred forty-nine participants were enrolled in the study and entered the lead-in placebo washout phase. Of these participants, 584 were randomized to the double-blind treatment phase, which was conducted at 47 sites. One hundred twenty-four, 121, 129, and 210 participants were randomized to the SLI381 30 mg/d, 20 mg/d, and 10 mg/d groups, and to the placebo group, respectively. The numbers of participants in each treatment group who completed the study were 112 (90.3%), 105 (86.8%), 119 (92.2%), and 173 (82.4%), respectively. The disposition of participants withdrawn from the study is shown in Table 1.

Across the treatment groups, the majority of participants were boys (72.9%–80.4%) and white (70.0%–82.1%) (Table 2). The mean age, weight, and height of these children were comparable across treatment groups. The majority (>90%) of the children were diagnosed as ADHD combined type in each of the treatment groups, and the distribution of the disorder types was balanced among the treatment groups. Although the study protocol called for only those with diagnoses of either combined or hyperactive subtypes to be eligible for participation, 12 participants diagnosed as inattentive were randomized to treatment. These participants were included in the efficacy and safety analyses because they represented only 2% of the total randomized and were distributed across all 4 groups. The average

<table>
<thead>
<tr>
<th>TABLE 1. Disposition of Participants Enrolled in the Study</th>
<th>Entire Study</th>
<th>Randomized Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dropout Before Randomization</td>
<td>SLI381 30 mg</td>
</tr>
<tr>
<td>Entered</td>
<td>649</td>
<td>65</td>
</tr>
<tr>
<td>Randomized</td>
<td>584</td>
<td>NA</td>
</tr>
<tr>
<td>Completed</td>
<td>509</td>
<td>NA</td>
</tr>
<tr>
<td>Discontinued</td>
<td>140</td>
<td>65</td>
</tr>
<tr>
<td>Reason</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Consent withdrawn</td>
<td>53</td>
<td>27</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>13</td>
<td>NA</td>
</tr>
<tr>
<td>Other*</td>
<td>33</td>
<td>26</td>
</tr>
<tr>
<td>Number of patients for assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy (ITT population)</td>
<td>563</td>
<td>NA</td>
</tr>
<tr>
<td>Safety</td>
<td>649</td>
<td>65</td>
</tr>
</tbody>
</table>

NA indicates not applicable.

* Including failure to meet entry criteria, noncompliance on scale assessments, and difficulty swallowing capsules.
duration of the disorder ranged from 2.5 to 2.9 years across the treatment groups, and 30.4% to 37.5% were treatment naïve.

Compliance
Noncompliance was defined as taking <80% or >120% of study medication during any outpatient evaluation period (visit to visit). For the ITT population, drug compliance among the treatment groups was similar across the 2 phases, ranging from 97.8% to 98.8% during the washout phase and from 97.2% to 98.2% during the double-blind treatment phase. Similar patterns were observed for the following subgroups: boys versus girls, age groups (6–8 years vs 9–12 years), race, and ADHD subtype.

Efficacy
Primary Efficacy: Teacher Ratings
The primary efficacy measure was the average of the CGIS-T total scores obtained at study endpoint, including both the morning and afternoon assessments, and the baseline score obtained during the placebo washout week was the covariate in the analytical model (Fig 2). Two-way analysis of variance showed a trend toward a difference across study sites in the baseline values ($P = .053$), but no difference in baseline scores across treatment groups ($P = .402$). All active treatment groups showed significant improvements in CGIS-T scores from baseline to study endpoint. The magnitude of changes from baseline to study endpoint was −6 to 1 in unit point for SLI381 groups compared with placebo, a roughly fivefold relative improvement of ADHD behavior at school in participants receiving active treatment. The 2-way ANCOVA at endpoint showed a highly significant treatment effect ($P < .0001$), a significant effect of baseline covariate ($P < .0001$), and site effect was not significant ($P = .2778$). Dunnett’s test, which adjusted the $P$ value for multiplicity, disclosed further that at the study endpoint, differences in CGIS-T total score were negative for each SLI381 dose group in comparison to placebo and highly significant ($P < .001$).

In addition, difference scores relative to placebo indicated a dose-response relationship for the SLI381 doses, with the largest improvement associated with the 30-mg group and the smallest improvement with the 10-mg group. Figure 3 illustrates the dose relationship between the 3 SLI381 treatment groups.

![Fig 2. CGIS-T total score average at baseline, study endpoint, and change for average of both morning and afternoon assessments. *$P < .001$ compared with placebo by Dunnett test following ANCOVA with baseline score as covariate.](image-url)
when the responses are corrected for the corresponding placebo response.

The CGIS-T total scores were also calculated separately for the morning and afternoon assessments (Table 3). The findings were very similar to the CGIS-T scores averaged across morning and afternoon, indicating that SLI381 doses from 10 to 30 mg per day were effective during both morning and afternoon.

The time course of improvements in each treatment group is depicted in Fig 4. The improvements in CGIS-T were consistent and dose-related at each treatment week as well as at study endpoint. Improvement during week 1 was similar between SLI381 treatment groups, and better than placebo group. During week 2, the 20-mg and 30-mg groups continued to improve, whereas the response of the 10-mg group remained relatively unchanged. During the third week the 30-mg group continued to improve, the improvements in the 10-mg and 20-mg groups showing a plateau effect. At all time points the improvements in the SLI381 treatment groups were statistically superior to the improvements in the placebo group.

For participants eligible for the ITT analysis, subgroup analyses of the CGIS-T total scores were performed for boys versus girls and for participants with and without previous stimulant therapy for ADHD. The trend of response to SLI381 treatment was similar among boys and girls and consistent with those of the entire ITT population. Patients who were naive to ADHD treatment responded as consistently and positively as those who were treated with stimulants before study participation.

### TABLE 3. Changes From Baseline to Study Endpoint for CGIS-T Total Score Average for Morning and Afternoon Assessments

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Morning Assessment</th>
<th>Afternoon Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change From Baseline</td>
</tr>
<tr>
<td>Placebo</td>
<td>10.1</td>
<td>-0.7</td>
</tr>
<tr>
<td>SLI381 10 mg</td>
<td>11.2</td>
<td>-5.0*</td>
</tr>
<tr>
<td>SLI381 20 mg</td>
<td>11.5</td>
<td>-5.4*</td>
</tr>
<tr>
<td>SLI381 30 mg</td>
<td>10.7</td>
<td>-5.8*</td>
</tr>
</tbody>
</table>

* P < .001 versus placebo using 2 sample t test (without Dunnett test).

Parent Ratings

The results of the parent evaluation, using the parent version of the CGIS, revealed similar efficacy (Fig 5; Table 4). The mean magnitude of changes from baseline to study endpoint was ~2.5 to 1 in unit point for SLI381 groups compared with placebo, a 1.5-fold relative improvement of ADHD behavior at home for participants on active treatment. The changes from baseline in the morning and late afternoon assessments were almost identical, indicating that the SLI381 was still effective in the early evening (defined as on and from 4:00 PM).

Global Assessments

Two other secondary measures which gave global assessments of overall improvement, one by the investigator (CGI) and the other by the parents (PGA), both showed the superiority of SLI381 therapy over placebo, and both confirmed the dose-response relationship between improvement and SLI381 dose (Fig 6).

Safety

Postrandomization, 263 (70.3%) SLI381-treated participants and 119 (56.7%) placebo-treated participants reported adverse events. The majority (69%) of adverse events were mild; 28% were moderate, and 4% were severe. The most frequently reported adverse events are shown in Table 5. Adverse events...
that occurred more frequently in the SLI381 groups were anorexia (21.9% vs 1.9% in the SLI381 and placebo groups, respectively), insomnia (16.6% vs 1.9%), abdominal pain (14.4% vs 9.5%), emotional lability (8.6% vs 1.9%), vomiting (7.2% vs 3.8%), and nervousness (5.6% vs 1.9%). Adverse events that had similar incidence rates with SLI381 and placebo treatment were headache (17.9% vs 21.4%), pharyngitis (7.0% vs 9.5%), and increased coughing (5.1% vs 5.2%). Severe adverse events reported after the start of double-blind therapy in 1% of participants were insomnia (1.6%), anorexia (1.3%), and emotional lability (1.1%), all of which occurred in SLI381-treated participants. There was no clear evidence for a dose-relationship in the incidence of adverse events across the 3 SLI381 treatment groups with the exception of anorexia.

Fifteen participants were withdrawn from the study during double-blind treatment because of adverse events (placebo: 6; SLI381–20 mg: 4; SLI381–30 mg: 5). Within the participants who were treated with SLI381, the adverse events that most frequently caused withdrawal included anorexia (3 participants), abdominal disturbances (2 participants), and nausea (2 participants).

The occurrence of abnormal laboratory values was low and similar in both placebo- and SLI381-treatment groups. No apparent trends were seen and most were considered to be clinically insignificant. No clinically significant changes in group mean ECG parameters were observed over the duration of the study; in all cases where abnormalities occurred, findings were deemed harmless, clinically insignificant, or normal by pediatric cardiologists. In regard to vital signs, no significant changes were seen between treatment groups and no significant changes occurred over time.

**DISCUSSION**

The primary objective of this study was to evaluate the efficacy and safety of SLI381, a single-dose, long-acting formulation of Adderall for the treatment of ADHD in naturalistic school and home settings. This study is one of the largest ADHD medication trials conducted to date, with efficacy assessments of nearly 600 patients. Overall, the findings from this study indicate that: 1) SLI381 10 mg per day gave a significant improvement in treatment of ADHD compared with placebo; 2) the maximum effect was reached within the first week of dosing; 3) dose increase by 10 mg at weekly intervals to a maximum

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**TABLE 4.** Changes From Baseline to Study Endpoint for CGI-S Total Score Average for Morning, Afternoon, and Late Afternoon Assessments

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Morning Assessment</th>
<th>Afternoon Assessment</th>
<th>Late Afternoon Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change</td>
<td>Baseline</td>
</tr>
<tr>
<td>Placebo</td>
<td>13.2</td>
<td>-1.7</td>
<td>13.7</td>
</tr>
<tr>
<td>SLI381 10 mg</td>
<td>12.4</td>
<td>-3.5*</td>
<td>12.5</td>
</tr>
<tr>
<td>SLI381 20 mg</td>
<td>13.1</td>
<td>-4.7†</td>
<td>13.0</td>
</tr>
<tr>
<td>SLI381 30 mg</td>
<td>12.5</td>
<td>-5.7†</td>
<td>13.0</td>
</tr>
</tbody>
</table>

*P* < .05 versus placebo using 2-sample *t* test (without Dunnett test).
† *P* < .001 versus placebo using 2-sample *t* test (without Dunnett test).

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**TABLE 5.** Percent Incidence of the Most Frequently Reported Adverse Events Postrandomization

<table>
<thead>
<tr>
<th>Adverse Event (COSTART Term)</th>
<th>Percentage of SLI381-Treated Participants Reporting (N = 374)</th>
<th>Percentage of Placebo-Treated Participants Reporting (N = 210)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Drug-Related or Possibly Related</td>
<td>All Drug-Related or Possibly Related</td>
</tr>
<tr>
<td>Anorexia</td>
<td>21.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Headache</td>
<td>17.9</td>
<td>13.9</td>
</tr>
<tr>
<td>Insomnia</td>
<td>16.6</td>
<td>16.6*</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14.4</td>
<td>11.5*</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>8.6</td>
<td>8.6*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7.2</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>7.0</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Nervousness</td>
<td>5.6</td>
<td>5.3</td>
</tr>
<tr>
<td>Nausea</td>
<td>5.1</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Increased cough</td>
<td>5.1</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

*P* < .05 compared with placebo treatment for drug-related or possibly related adverse events.
of 30 mg per day resulted in further improvements that occurred within the first week of each increase in dose; 4) participants treated with SLI381 30 mg per day showed approximately a 5 unit points relative improvement in ADHD behavior, as measured by CGIS-T, over those receiving placebo; and 5) SLI381 was well tolerated. These results document that SLI381 is a safe and effective once-daily dosage form of stimulant medication that lasts throughout the school day and into the early evening.

The findings that one early morning dose of SLI 381 was effective throughout the morning and afternoon as reported by parents and teachers confirm, in the naturalistic setting of home and school, previous results in a laboratory setting.26,27 The previous study examined pharmacokinetic and pharmacodynamic parameters of three fixed doses of SLI381 compared with placebo and Adderall 10 mg in an analog classroom setting and found SLI381 20 mg and 30 mg to produce rapid improvements in behavior and cognition by 1.5 hours postdose. These improvements were sustained for up to 12 hours, strongly supporting a duration of action that covers the school day.

The long acting clinical effects of SLI381 clearly eliminate the need for in school administration. Considering the inherent problems associated with in-school dosing of stimulant medications for ADHD (ie, many schools do not have nursing staff available to administer these medicines; many parents and children do not want to receive their treatment in school because of the potential stigmatizing effects of such procedures; and the medicolegal concerns associated with the storage and administration of scheduled medicines in school) the availability of a safe and effective long acting stimulant such as SLI381 is likely to greatly facilitate the treatment of the large number of afflicted youth with ADHD.

Such benefits of SLI381 not only will increase patient privacy and compliance, but are also important to secure a steady clinical effect throughout the school day. Despite the well-documented efficacy of stimulant drugs in the treatment of ADHD, the short duration of action of the immediate release preparations has been associated with therapeutic peaks and valleys with their potential for breakthrough symptoms in between doses and likely adverse impact on treatment satisfaction.

Of equal clinical relevance is the finding documenting that the clinical benefits of SLI381 extend beyond the school day to include time-points after 4:00 PM. Such results indicate that the duration of action of SLI381 should allow for pharmacological support of homework activities, after school athletic and social activities, as well as family life—critical components of the child’s life.

A clear dose-response relationship was evident across all efficacy assessments, with increased improvement at successive increases in dose. In fact, the main efficacy endpoint, the CGIS-T total score average, reached normalized values for the SLI381 30-mg group. In the absence of dose-limiting adverse effects when treating patients with ADHD, much thought should be given to increasing the dose to an optimal level. Although lower doses may not be subtherapeutic, this study demonstrates that optimal results were seen at the 30-mg dose of SLI381.

Study medication was very well tolerated and the incidence of adverse events compares favorably with that of immediate-release compounds. There was little evidence of a dose-response relationship in safety parameters across the SLI381 treatment groups. Thus, increasing the dose had no apparent influence on tolerability. The exception to this may be in the incidence of reported anorexia. However, posthoc analysis of reported anorexia showed that treatment naïve participants had significantly more problems with this (33.6% reporting) than did those participants with prior experience with ADHD medications (16.2% reporting). Because this was a short-term trial of 3 weeks duration, it can not be determined from these data whether the reported incidence of this adverse event would abate over time. A 24-month, open-label trial is ongoing and may better define the long-term adverse event profile of this medication.

Noteworthy is the clean cardiovascular profile of SLI381 as evidenced by repeated ECG measurements. This is important to emphasize in light of recent concerns regarding potential cardiovascular effects of stimulant medications.

Subgroup analyses showed the same, positive improvements for boys and girls with ADHD. In fact, considering the sizeable representation of girls, this study represents one of the largest clinical trials of girls with ADHD ever conducted. Although almost all of the available literature on ADHD is limited to boys with this disorder, recent work documents that ADHD is equally disabling in boys and girls with ADHD.21 Thus, the findings of similar benefits associated with SLI381 treatment in boys and girls with ADHD are very encouraging and extend to females the well-documented therapeutic benefits of psychostimulants in the treatment of ADHD.

Although the majority of patients in this study had previous exposure to stimulant medication, a substantial minority (~34%) were treatment naïve. The subgroup analyses showed the same, positive improvements for patients with a history of stimulant treatment as for those with no previous exposure to stimulant medication. This demonstrates the efficacy of SLI381 across both patient groups.

Because our sample included a narrow developmental window of children 6 to 12 years, it is unclear whether our results will generalize to older age groups. Considering the wide range of benefits associated with the long duration of action of SLI381, it is likely that other age groups will also benefit from this pharmacologic profile. Clearly, additional clinical trials are needed to document the efficacy and safety of SLI381 in adolescents and adults with ADHD.

Only a very small number of participants had ADHD inattentive type, making it difficult to draw any conclusions regarding this subset of patients. Although stimulant medications are commonly used and effective in these patients, additional studies are needed to accurately assess the effects of SLI381 in this patient group.
CONCLUSION
SLI381 is a safe and efficacious treatment in children for the treatment of ADHD. The extended-release nature of this new formulation of mixed amphetamine salts allowed adequate control of the signs and symptoms of ADHD using a once-a-day dosing schedule. Dose-related improvements in children’s behavior at school and home when compared with placebo were seen after the administration of 1 SLI381 dose of 10 mg to 30 mg in the morning, in both morning and afternoon as measured by both teacher and parent rating scales, and continued into late afternoon as measured by parent ratings. SLI381 was effective in participants with previous experiences of stimulant treatment for ADHD, and in participants who were naïve to ADHD treatment. The use of this extended-release formulation would simplify medication schedules for children who are in school, and could improve compliance. Dosing in the morning before the child left for school would ensure protection against ADHD symptoms during and beyond the school day.

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**MEDICAL STUDENTS SUE OVER RESIDENCY SYSTEM**

“A class-action lawsuit to be filed in Washington challenges the matching program on antitrust grounds. The suit says the defendants, including 7 medical organizations and more than 1,000 private hospitals, have used the program to keep residents’ wages low and hours long. Almost all first-year residents make less than $40,000 a year and often work 100-hour weeks.

If the suit is successful, the nation’s health care system faces an enormous financial liability and the prospect of being forced to change the way that generations of doctors have been trained.

More than 80% of first-year residency positions are offered exclusively through the program, known formally as the National Resident Matching Program. The matches are based on ranked lists submitted by hospitals and the 15,000 or so students, and both sides agree in advance to accept the match. . . There is no room for negotiations about wages, hours, or other terms of employment. As a consequence, the plaintiffs say, the hospitals, which share detailed salary information with each other, can force residents to accept below-market wages for 3 to 8 years, depending on specialty, of their residencies.

The stakes in the new suit are high. The complaint does not specify how much money the plaintiffs seek, but they claim to represent a class of 200,000 residents. If residents’ fair market salaries were determined to be $100,000, say, the sums at issue for a single year would exceed $12 billion, and because this is an antitrust case, the damages would be automatically tripled.”

*New York Times*. May 7, 2002

Noted by JFL, MD
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of SLI381 (Adderall XR) in Children With Attention-Deficit/Hyperactivity Disorder

Joseph Biederman, Frank A. Lopez, Samuel W. Boellner and Mark C. Chandler

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DOI: 10.1542/peds.110.2.258

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