

**MEMORANDUM      DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**DATE:**                    **March 3, 2006**

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**FROM:**                    Andrew Mosholder, M.D., M.P.H., Epidemiologist

**SUBJECT:**              Psychiatric Adverse Events in Clinical Trials of Drugs for  
Attention Deficit Hyperactivity Disorder (ADHD)

**PID:**                        D060163

**DRUGS:****Table 1. Drugs indicated for ADHD included in this review**

<b>Approved Products</b>			
<b>NDA #</b>	<b>Name</b>	<b>Company</b>	<b>Date of Approval</b>
21-303	Adderall XR (mixed salts of a single entity amphetamine product) Extended-Release Capsules	Shire Pharmaceuticals, Inc.	10/11/2001
21-278	Focalin (dexamethylphenidate HCL) Tablets	Novartis Pharmaceuticals Corporation	11/13/2001
21-802	Focalin XR (dexamethylphenidate HCL) Extended-Release Capsules	Novartis Pharmaceuticals Corporation	5/26/05
21-121	Concerta (methylphenidate HCL) Extended-Release Tablets	McNeil Consumer and Specialty Pharmaceuticals	8/11/2000
21-259	Metadate CD (methylphenidate HCL) Extended-Release Capsules	UCB Pharma, Inc.	4/3/2001
21-284	Ritalin LA (methylphenidate HCL) Extended-Release Capsules	Novartis Pharmaceuticals Corporation	6/5/2002
21-411	Strattera (atomoxetine HCL) Capsules	Eli Lilly & Company	11/26/2002
<b>Pending NDAs/sNDAs</b>			
20-717 S-019	Provigil (modafinil) Tablets	Cephalon, Inc.	pending
21-514	Methylphenidate transdermal system (MTS)	Noven Pharmaceuticals, Inc (Shire is a co-development partner with Noven)	pending

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## 1 EXECUTIVE SUMMARY

In follow-up to the June 2005 Pediatric Advisory Committee meeting discussion of adverse events with Concerta, it was decided to conduct a review of psychiatric adverse events with drugs for attention deficit hyperactivity disorder (ADHD). Results of the analysis of postmarketing reports will be presented separately. This consult summarizes the data from approximately 90 clinical trials that was submitted in response to the agency's request. Sponsors of marketed products for ADHD and drugs under review for that indication were asked to search their clinical trial databases for adverse psychiatric events in three primary categories: psychosis and mania, suicidal events, and aggression. This search was conducted electronically using selected, prespecified adverse event terms. They were also asked to search their databases for additional miscellaneous psychiatric events if the outcome was serious. Data on the duration of exposure to treatment in the trials and subject characteristics were also requested, as were clinical descriptions of the events and descriptions of the clinical trials in the ADHD development programs. Data were pooled within development programs to estimate the rates of the events of interest. The findings are subject to the usual limitations of such safety analyses, which include potential lack of consistency of ascertainment of adverse events across the various trials, the possibility of misclassification of cases, and statistical power limitations imposed by the sample sizes.

With these limitations in mind, specific observations about these clinical trial data are as follows. With respect to the clinical trial design, a large number of the controlled trials required subjects who were known to respond to stimulants, or who had no history of intolerance to stimulants. Also, many of the controlled trials were of very short duration. These factors limit the utility and external generalizability of the safety datasets obtained from the trials. With respect to specific findings, suicidal events were more frequent with atomoxetine and modafinil treatment than with placebo. It should be noted that there were no completed suicides in ADHD trials with these drugs (one completed suicide was reported in a placebo patient in an atomoxetine trial for another indication). Aggressive events were more frequent with the methylphenidate transdermal patch, and to a lesser degree with atomoxetine, than with placebo. None of these imbalances in rates reached customary levels of statistical significance in this analysis, although Lilly's previous analysis of suicidal events with atomoxetine did show a statistically significant association. For aggression events, there was little evidence in these trials that drug treatment reduced their frequency relative to placebo; only for modafinil was the event rate numerically lower than for placebo and this was not statistically significant. With respect to psychosis and mania events, although the numbers of such events with drug treatment were small, the complete absence of such events with placebo treatment was notable. For 4028 pediatric ADHD patients in these trials, there were no such events in 425 person-years of aggregated placebo treatment. Similarly, there were no psychosis or mania events in these trials among adult ADHD patients receiving placebo. Psychosis/mania events occurred during double-blind treatment with every compound except Adderall XR (although there were psychosis/mania events with open label

Adderall XR treatment). Furthermore, as noted above, some subjects in Phase I studies of these drugs experienced this type of event.

Patients and physicians should be aware of the possibility that these events, when they arise in the course of drug treatment of ADHD, may represent adverse reactions to drugs. In terms of future clinical trial designs, it should be borne in mind that short-duration trials and trials which exclude subjects who are naïve to this class of drug, while they may be efficient for determining efficacy, have limitations for defining the safety profile of the drug.

## **2 BACKGROUND**

The present effort to characterize psychiatric adverse events among patients treated with drugs for attention deficit hyperactivity disorder (ADHD) arose from a discussion at the June 30, 2005 meeting of FDA's Pediatric Advisory Committee. The rationale for this project was summarized in the letter FDA's Division of Psychiatry Products sent to the sponsors of products for ADHD, in September 2005:

At a June 30, 2005 meeting of the Pediatric Advisory Committee, a concern was raised about reports of psychiatric adverse events occurring in patients being treated with various drug products for ADHD. The reports considered at that meeting were for the drug Concerta, but it was acknowledged that similar reports have been made for other ADHD products. Although some psychiatric adverse events are already mentioned in the labeling for various ADHD products, there was general support for the view that labeling may need to be enhanced to better characterize these events. However, there was also agreement that such labeling changes should await a more comprehensive review of psychiatric events for ADHD products. In order to facilitate this more comprehensive review, we are requesting psychiatric adverse event data for various products approved for the treatment of ADHD.<sup>1</sup>

An analysis of postmarketing reports of adverse psychiatric events will be presented in a separate document. This document will present data on the psychiatric adverse events of interest from the clinical trial programs for the various ADHD products.

## **3. METHODS**

In the Information Request letters sent to the sponsors of ADHD drugs, the Division of Psychiatry Products asked the sponsors to conduct a search of their clinical trial databases for the adverse events of interest. The primary categories of adverse events to be analyzed were (1) psychosis and mania; (2) suicidal events; and (3) aggression. In addition, sponsors were asked to provide data on serious adverse events (i.e., those meeting the regulatory criteria for "serious") for a variety of miscellaneous psychiatric outcomes. Sponsors were to perform a string search of their electronic clinical trial databases for both preferred adverse event terms (e.g., MedDRA, COSTART) and investigator verbatim terms that might reflect one of the categories of interest. The

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<sup>1</sup> Dr. Thomas Laughren, FDA Division of Psychiatry Products, September 14, 2005.

following table lists the event terms suggested in FDA’s request. The complete letter is reproduced in the consult describing postmarketing reports of these adverse events.<sup>2</sup>

**Table 2. Psychiatric event terms recommended for search by FDA**

Psychosis/mania	Suicidal ideation and behavior	Aggression and violent behavior	Miscellaneous (serious outcome only)
<ul style="list-style-type: none"> <li>o Hallucination (any type, including visual, auditory, tactile, mixed, etc)</li> <li>o Delusion (any type including somatic, persecutory, grandeur, reference)</li> <li>o Schizophrenia (any type)</li> <li>o Psychotic disorder</li> <li>o Transient psychosis</li> <li>o Acute psychosis</li> <li>o Paranoia</li> <li>o Childhood psychosis</li> <li>o Schizophreniform disorder</li> <li>o Schizoaffective disorder</li> <li>o Catatonia</li> <li>o Mania</li> <li>o Hypomania</li> </ul>	<ul style="list-style-type: none"> <li>o Depression suicidal</li> <li>o Gun shot wound</li> <li>o Intentional self-injury</li> <li>o Non-accidental overdose</li> <li>o Overdose</li> <li>o Self injurious behavior</li> <li>o Self injurious ideation</li> <li>o Self-mutilation</li> <li>o Suicidal ideation</li> <li>o Suicide attempt</li> <li>o Completed suicide</li> </ul>	<ul style="list-style-type: none"> <li>o Aggression</li> <li>o Anger</li> <li>o Hostility</li> <li>o Homicidal ideation</li> <li>o Sexual offense</li> <li>o Murder</li> <li>o Imprisonment</li> </ul>	<ul style="list-style-type: none"> <li>o Abnormal behavior</li> <li>o Agitation</li> <li>o Amnesia</li> <li>o Confusional state</li> <li>o Depressed mood</li> <li>o Depression</li> <li>o Disorientation</li> <li>o Emotional disorder</li> <li>o Emotional distress</li> <li>o Feeling abnormal</li> <li>o Memory impairment</li> <li>o Mood altered</li> <li>o Mood swings</li> <li>o Personality change</li> <li>o Thinking abnormal</li> <li>o Anxiety</li> <li>o Fearfulness</li> <li>o Phobia</li> <li>o Panic attack</li> <li>o Sleep disturbance</li> <li>o Tics</li> <li>o Obsessive or compulsive behavior</li> <li>o Trichotillomania</li> </ul>

The sponsors were instructed to enumerate events in these categories for both open label and double blind clinical trials. Events occurring either within 48 hours of the end of study treatment or within 30 days of the end of study treatment were to be enumerated separately. The sponsors were asked to provide synopses of the clinical trials, to assist in classifying the type of study for the purpose of aggregating data across trials. Sponsors were also asked to stratify data from their trials by age and gender subgroups, and to provide the duration of treatment (person-days) for each age and gender strata by trial, along with a count of patients who had events meeting the criteria for one of the categories of interest. However, we found that in some cases sponsors provided exposure time in person-days for each dose administered during the trial, resulting in the counting of some patients more than once according to how many doses they had received in that trial. In such instances the number of patients treated in the trial was determined from the clinical trial synopsis. Clinical trial exposure was to be classified as open label extension, open label run-in, or double blind. Patients with more than one event were to be counted only once per trial per category. In addition, the sponsor was asked to provide an

<sup>2</sup> PID D050243

accompanying listing of patients who had such events, with clinical information including patient characteristics, dose, concomitant medications, whether the event required discontinuation of treatment, and whether the event met criteria for “serious.” (However, some sponsors provided this listing without specifying the category in which the event had been counted, making it difficult to reconcile the summary data with the listing of individual events.) Sponsors were also requested to provide clinical summaries of cases involving a serious outcome or premature discontinuation of treatment.

The drug products included in this analysis are those listed at the beginning of this document. All sponsors provided the requested data.

The submitted data were reviewed and data on the frequency of events were aggregated across trials within each product’s clinical development program. Pooling across development programs was avoided because of apparent differences between the several development programs in patient populations and ascertainment of the selected adverse events. The event data were too sparse to permit a meaningful meta-analysis stratified by trial, as there were many trials with no events. However, the pediatric placebo exposure was aggregated to provide an estimate of the rates of events in a cohort of unmedicated pediatric ADHD patients. Statistical computing was accomplished with Microsoft Excel, JMP 5.1, and Stata 7.0.

## **4. RESULTS**

### **Summary results**

The data requests yielded data on 100 separate clinical trials in the development programs for these products. The table on the following page presents an overview of the clinical trials and the events. Note that this table includes all age groups and omits active control treatments for simplicity.

**Table 3. Summary of ADHD clinical trials and psychiatric adverse events (all age groups)**

Drug	Type of trial	No. of Trials	Duration of trials (range)	Category of exposure	N	Patient-years	Psychosis /mania events	Suicidal events	Aggression events
Concerta	DB	4	6-28 dys	Placebo	317	10.20	0	0	0
				Drug DB	321	12.68	0	0	0
	OL	7	≤ 12 mos.	Drug OL	2824	1397.40	8	6	52
Metadate CD	DB	4	7-21 dys	Placebo	572	19.44	0	0	3
				Drug DB	493	19.13	0	0	3
	OL	2	NS	Drug OL	322	19.55	0	0	6
MTS	DB	8	1-49 dys	Placebo	464	23.84	0	0	1
				Drug DB	471	30.26	4	0	6
	OL	4	NS	Drug OL	617	341.97	6	1	7
Modafinil	DB	6	1-9 wks	Placebo	366	39.87	0	0	5
				Drug DB	772	85.50	2	4	9
	OL	3	≤1 yr	Drug OL	924	383.53	2	0	14
Adderall XR	DB	7	1-4 wks	Placebo	678	28.00	0	0	6
				Drug DB	1236	77.18	0	1	20
	OL	6	≤2 yrs	Drug OL	5177	1767.47	14	8	166
Atomoxetine	DB	20	≤78 wks	Placebo	1443	350.73	0	4	18
				Drug DB	2459	654.87	4	9	49
	OL	10	≤ 96 wks	Drug OL	5270	5095.27	12	44	198
Ritalin LA	DB	5	1-14 dys	Placebo	259	11.31	0	1	0
				Drug DB	383	25.66	2	0	2
	OL	1	NS	Drug OL	125	25.95	0	1	0
d-MPH	DB	8	≤49 dys	Placebo	468	53.24	0	0	0
				Drug DB	588	64.75	4	0	1
	OL	5	≤ 1 yr	Drug OL	740	362.09	3	1	13

Abbreviations: DB double blind, OL open label, NS not specified, MTS methylphenidate transdermal system, d-MPH dextromethylphenidate

## Summary of comparison of rates in double blind, pediatric trials

The following summary table displays the comparisons between the drug products and placebo for the three categories of events, within each development program, for pediatric subjects. Active controls were omitted from this summary. At the bottom of the table the pooled results for placebo are shown.

**Table 4. Summary of double blind trial data for pediatric subjects**

Treatment	N	Person- yrs	Psychosis/ mania events	Suicidal events	Aggression events	Psychosis/ mania events/ 100 pt-yrs	Suicidal events/100 pt-yrs	Aggression events/100 pt-years
Placebo	317	10.2	0	0	0	0.00	0.00	0.00
Concerta	321	12.68	0	0	0	0.00	0.00	0.00
Placebo	572	19.44	0	0	3	0.00	0.00	15.43
Metadate CD	493	19.13	0	0	3	0.00	0.00	15.68
Placebo	464	23.84	0	0	1	0.00	0.00	4.19
MTS	471	30.26	4	0	6	13.22	0.00	19.83
Placebo	308	32.55	0	0	5	0.00	0.00	15.36
Modafinil	664	75.11	2	4	9	2.66	5.33	11.98
Placebo	599	23.34	0	0	6	0.00	0.00	25.71
Adderall XR	1026	63.78	0	1	18	0.00	1.57	28.22
Placebo	1056	256.02	0	3	15	0.00	1.17	5.86
Atomoxetine	1939	524.64	4	8	45	0.76	1.52	8.58
Placebo	259	11.31	0	1	0	0.00	8.84	0.00
Ritalin LA	383	25.66	2	0	2	7.79	0.00	7.79
Placebo	415	48.47	0	0	0	0.00	0.00	0.00
d-MPH	420	49.73	1	0	0	2.01	0.00	0.00
Placebo (Pooled across drugs)	3990	425.11*	0	4	30	0	0.94	7.06

\*Age categories varied slightly by sponsor, but subgroup exposures may be summarized as follows: adolescent males 58 pyrs. adolescent females 18 pyrs, male children 274 pyrs, female children 75 pyrs.

## Summaries of psychiatric adverse events by clinical development program

In the following pages, the findings with respect to the psychiatric adverse events of interest are presented for each drug product.

### A. Concerta (NDA 21-121, McNeil)

Concerta is an extended release formulation of methylphenidate marketed by McNeil. Safety and efficacy studies contributing data to this analysis are summarized in Appendix Table A. Omitted from the analysis were studies in which the primary focus was on clinical pharmacology or bioavailability. Also, McNeil omitted from their response data from studies in which no Concerta was administered; i.e., involving non-Concerta formulations of methylphenidate only. In addition, there were a total of 17 non-U.S. studies of Concerta for which only limited data were available, and these have been omitted from the analysis. (The information currently available to the sponsor indicates no adverse events of interest occurred among subjects in these trials, but data are incomplete.)

It will be noted from the appendix table that all of the double blind exposure to Concerta in these trials occurred among patients who were already methylphenidate users, or had undergone open label treatment with methylphenidate prior to randomization (i.e., in study 011146).

The table below provides a summary of the adverse events of interest in the safety and efficacy trials with Concerta. There was only one relevant event during double blind treatment, an aggression event associated with use of Ritalin as an active control.

**Table A. Frequency of patients experiencing selected psychiatric events in Concerta clinical safety and efficacy studies.**

Study design	Treatment	Person- yrs	Person- yrs	Psychosis/ mania events	Suicidal events	Aggression events
DB	Placebo	317	10.20	0	0	0
DB	Concerta	321	12.68	0	0	0
DB	Ritalin	236	9.69	0	0	1
OL	Concerta	2824	1397.40	8	6	52
OL	Ritalin	76	11.81	0	0	4
OL	Atomoxetine	472	27.94	1	0	4
OL run in	Concerta	330	16.96	1	1	3

Five of the 52 aggressive events occurring during open label Concerta treatment were deemed serious.

The only study to enroll adult (>18 years old) ADHD subjects was open label study C99018, and in that study there were no events from these three categories among the adult subjects.

There were no miscellaneous adverse events deemed “serious” during double blind treatment. During open label treatment, one atomoxetine treated subject (172101 in study 12101) developed severe fearfulness that was considered serious, and Concerta-treated patient 19603 in the same study developed emotional distress that was considered serious and persisted post-treatment (see below). This patient, an 11-year old boy, was psychiatrically hospitalized and was eventually diagnosed with bipolar disorder, mixed with psychotic features.

There were a few relevant adverse events observed post-treatment (these are not shown in the table above). No events meeting the search criteria occurred within 48 hours of treatment discontinuation in these trials. With respect to events occurring between 48 hours and 30 days after treatment discontinuation, one subject became delusional five days after discontinuing Concerta, one subject was hospitalized for depression with a suicidal attempt 25 days after discontinuing Concerta, and in the “Miscellaneous” category, subjects 19603 (see above) and 19604 in open label study 12101 experienced “emotional distress” that was considered a serious adverse event 23 and 20 days, respectively, after study treatment ended. The narrative for patient 19604 also noted violent behaviors requiring psychiatric hospitalization, although the event was not categorized under aggression; the patient’s diagnoses included bipolar disorder and intermittent explosive disorder.

## **B. Metadate CD (NDA 21-259, UCB Pharma, Inc.)**

Metadate CD is an extended release preparation of methylphenidate. The sponsor’s development program included 4 randomized, double blind efficacy trials and 2 open label safety trials; only pediatric subjects were enrolled in Metadate CD safety and efficacy trials. Appendix table B provides an overview of the clinical trials for studies in ADHD patients. All double-blind trials enrolled subjects who had been treated previously with methylphenidate. The sponsor’s search for the adverse psychiatric events of interest yielded no psychosis or mania events, no suicidal events, and 6 aggression events in double blind trials (3 each with Metadate and placebo). There were an additional 6 aggression events with open label treatment. All of the aggression events in both double blind and open label studies occurred in boys. There was only one serious psychiatric adverse event in these studies, in a Metadate-treated patient (termed “abnormal behavior”) which resulted in hospitalization (Study CD00500 / Patient #2003). This event was counted as aggression, in the open-label trial category.

There were no relevant psychiatric events in the sponsor’s bioavailability/pharmacokinetic trials, and no relevant events were reported up to 30 days post-treatment.

The following is a summary of the exposures and events in the Metadate CD safety and efficacy clinical trial program.

**Table B. Frequency of patients experiencing selected psychiatric events in Metadate CD clinical safety and efficacy studies.**

Study design	Treatment	Person- yrs	Psychosis/mania events	Suicidal events	Aggression events	
DB	Placebo*	572	19.44	0	0	3
DB	Metadate CD	493	19.13	0	0	3
DB	Ritalin	158	7.61	0	0	0
DB	Concerta	180	3.29	0	0	0
OL	Metadate CD	322	19.55	0	0	6

\*includes single-blind placebo treatment in study MAI00104

In addition to the events enumerated above, patient 11-218 in study CD00600 experienced euphoria on the first day of treatment with placebo, and patient 1-10 in study CD00700 experienced euphoria on day 1 of Metadate CD, but these events were not included in the category of psychosis/mania as enumerated above.

### C. Methylphenidate transdermal system (MTS) (Noven, NDA 21-514)

The methylphenidate transdermal system (MTS) is a patch that delivers methylphenidate through the skin and is worn throughout the day and removed in the evening. This product is not yet approved. The development program included 8 randomized efficacy trials and 3 completed open label safety trials. All ADHD safety and efficacy trials involved only pediatric subjects. The characteristics of these trials are summarized in Appendix table C, and the summary data on psychiatric adverse events of interest are summarized in the table below.

**Table C. Frequency of patients experiencing selected psychiatric events in MTS clinical safety and efficacy studies.**

Study design	Treatment	N	Person- yrs	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	464	23.84	0	0	1
DB	MTS	471	30.26	4*	0	6**
DB	Ritalin	10	0.19	0	0	0
DB	Concerta	91	11.10	1	0	1
Open	MTS	617	341.97	6	1	7

\*Rate ratio undefined, rate difference 0.13/person year, p-value versus placebo 0.10 (Stata version 7.0)

\*\*Rate ratio versus placebo 4.7, p-value 0.13 (Stata version 7.0).

Of the four psychosis/mania events during double blind treatment, two involved hallucinations, one a manic episode with hallucinations, and one paranoia. Two of the 7 aggression events occurring during open label treatment met criteria for “serious.” Although none of the 6 aggression events during double blind treatment met criteria for serious, one did result in a suspension from school.

Additionally, in study SPD485201 there was an open-label run-in period prior to randomization that enrolled 93 patients (80 eventually were randomized), and during this run-in period there were 2 aggression events.

There were also clinical data from 9 bioavailability studies (4 involving pediatric ADHD patients), and 2 special skin sensitization studies in healthy adults. Review of the sponsor's listing of adverse events showed that in the biopharmaceutics trials, one child receiving Concerta, and 1 adult administered MTS buccally experienced psychosis/mania events. In the two open-label special skin sensitization protocols, which together exposed 315 healthy adult volunteers, there were 6 psychosis/mania events and one aggression event. Data from a special study of abuse potential in adults (N17-007) showed 2 psychosis/mania events with MTS, and four such events with the active controls.

The sponsor identified no relevant adverse events occurring after treatment discontinuation. Also, there were no serious psychiatric adverse events in the miscellaneous category.

#### **D. Modafinil (NDA 20-717 S-019, Cephalon, Inc.)**

Modafinil (Provigil, marketed by Cephalon, Inc.) is a non-sympathomimetic stimulant marketed for the treatment of excessive daytime sleepiness associated with sleep disorders. An indication for ADHD is under review, and will be the topic at the March 23 Psychopharmacologic Drugs Advisory Committee meeting.

With respect to psychotic adverse reactions, the current modafinil labeling notes (in the Precautions section) one such episode in a normal volunteer:

One healthy male volunteer developed ideas of reference, paranoid delusions, and auditory hallucinations in association with multiple daily 600 mg doses of PROVIGIL and sleep deprivation. There was no evidence of psychosis 36 hours after drug discontinuation.<sup>3</sup>

#### Analysis of Psychiatric Adverse Events in Response to Approvable Letter

The sponsor provided the following analysis in reply to our September 14, 2005 request as part of their response to the approvable letter for the indication of ADHD.

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<sup>3</sup> Provigil prescribing information available at [www.provigil.com](http://www.provigil.com)

**Table D1. Frequency of patients with psychiatric adverse events in ADHD trials (response to approvable letter)**

Study design	Treatment	N	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	308	0	0	5
DB	Modafinil	664	2	4	9
Open	Modafinil	799	2	0	14

Analysis in response to FDA request 9-14-05

The sponsor also provided data on the adverse events of interest in a separate submission 1-6-06, responding specifically to the agency's request letter of 9-14-05. It appeared that this later submission included additional clinical trial data, although a list of the specific studies included was provided only for the 1-6-06 submission, so this could not be verified.

**Table D2. Frequency of patients with psychiatric adverse events in ADHD trials (sponsor's 1-6-06 submission)**

Study design	Treatment	N	Patient years of exposure	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	366	39.87	0	0	5
DB	Modafinil	772	85.50	2	4	9
Open	Modafinil	924	383.53	2	0	14

There were no serious adverse events in the miscellaneous category.

There were more events in all categories among modafinil treated patients compared to placebo, but the exposure to modafinil was greater. It will be noted, however, that the frequency of these events during double blind treatment was higher than during open label treatment.

The table below displays the data for the subgroup of pediatric patients only (i.e., eliminating study 205 in adults, in which there were no events of interest).

**Table D3. Frequency of pediatric patients with psychiatric adverse events in ADHD trials (from 1-6-06 submission)**

Study design	Treatment	N	Patient years of exposure	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	308	32.55	0	0	5
DB	Modafinil	664	75.11	2	4	9
Open	Modafinil	799	369.35	2	0	14

It should be noted that the NDA review by the Division of Psychiatry Products identified two additional probable cases of aggression during double blind treatment, in study 207 (patients 410 and 411).<sup>4</sup>

<sup>4</sup> Drs. June Cai and Glenn Mannheim, Division of Psychiatry Products

In addition, the sponsor noted that there were no events in the miscellaneous category that met criteria for “serious.”

With respect to events occurring after study treatment, one modafinil-treated subject (#410 in study 207) experienced formication (coded as psychosis) within 48 hours of treatment discontinuation, and one 6-year old female (subject 312-014016) was hospitalized for self-harmful behavior (putting a rope around her neck) two days after discontinuing open label treatment with modafinil. There were no psychiatric adverse events during the period from 48 hours to 30 days after treatment discontinuation.

One of the two psychosis/mania events during open label treatment required psychiatric hospitalization for a psychotic episode with suicidal ideation (patient 213-11002, an 8-year old boy who had a history of such symptoms, although this was apparently not known at study entry). This case was counted by the sponsor only in the psychosis/mania category, although it perhaps could have been counted as a suicidal event as well. The only two patients with serious psychiatric adverse events in these clinical trials were 312-014016 and 213-11002. (An additional case of suicidal ideation in a modafinil treated patient, requiring hospitalization, was included in the sponsor’s safety update for the ADHD supplement (patient 016001 from ongoing Study 312), but this apparently occurred after the cutoff date for the present data set.<sup>5</sup>)

Appendix table D displays the characteristics of the ADHD clinical trials. In addition, the sponsor provided data on the psychiatric events of interest from other indications. These data are summarized below.

**Table D4. Frequency of patients with selected psychiatric adverse events in studies of other indications**

Study design	Indication	Treatment	Patient years of exposure	Psychosis/mania events	Suicidal events	Aggression events	Miscellaneous serious events
DB	Excessive sleepiness	Placebo	96.65	1	0	0	1
DB	Excessive sleepiness	Modafinil	168.44	3	1	4	2
Open	Excessive sleepiness	Modafinil	1988.31	4	6	17	4
DB	Other*	Placebo	26.56	0	0	0	0
DB	Other*	Modafinil	98.37	8	2	13	6
Open	Other*	Modafinil	89.98	10	3	12	3

\*Clinical pharmacology, depression, dementia, head trauma, and other disorders

<sup>5</sup> Dr. June Cai, FDA Division of Psychiatric Products, personal communication

### E. Adderall XR (NDA 21-303, Shire)

Adderall and Adderall XR are formulations of mixed amphetamine salts. The active ingredient is a mixture of 25% l-amphetamine and 75% d-amphetamine. Adderall XR is an extended release, once-a-day formulation. There were no clinical safety and efficacy trial data available for Adderall, so the results below are for Adderall XR exclusively.

The Adderall XR development program included 3 randomized, double blind, placebo controlled trials in pediatric patients and one in adult ADHD patients. The Adderall XR safety and efficacy trials are summarized in Appendix table E.

The table below displays the summary data for the psychiatric events of interest.

**Table E1. Frequency of patients experiencing selected psychiatric events in Adderall XR clinical safety and efficacy studies.**

Study design	Treatment	N	Person-yrs	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	678	28.00	0	0	6
DB	Adderall XR**	1236	77.18	0	1	20
Open	Adderall XR	5177	1767.47	14	8	166
DB	Atomoxetine	108	4.83	1	0	1

\*N not available \*\*includes 48 subjects in study 201 who received both Adderall and Adderall XR

The table below shows the data for the subgroup of trials involving only subjects of pediatric age.

**Table E2. Frequency of patients experiencing events in pediatric trials**

Study design	Treatment	N	Person-yrs	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	599	23.34	0	0	6
DB	Adderall XR*	1026	63.78	0	1	18
Open	Adderall XR	4233	1280.80	9	8	150
DB	Atomoxetine	108	4.83	1	0	1

\*includes 48 subjects in study 201 who received both Adderall and Adderall XR

There were relatively few events in the categories of psychosis/mania and suicidal events in the double blind trials. There were somewhat more aggression events, but the distribution of events between drug and placebo was roughly proportional to the exposures. Of the 26 aggression events during double blind treatment, 11 occurred in study 201, a laboratory school study. Conceivably, closer observation of the subjects in that setting might have led to more reports of aggressive behaviors.

One trial included in the data above involved pediatric patients with Oppositional Defiant Disorder. Although the data were included in the totals above, they will be noted here

separately since this is a different albeit related indication. Study 311 was a 4 week randomized, double blind, placebo controlled, parallel group study involving five treatment arms (four fixed doses of Adderall XR and placebo). There was one aggression category event among the 60 patients who received placebo, and one suicidal event and seven aggression events among the 237 patients treated with Adderall XR. The pattern of events did not appear dose-related.

The sponsor reported no adverse events of interest in any Phase 1 trials.

With respect to events occurring after the end of treatment, there were a total of 4 subjects with such events. Patient 027-002 in study 311, a 17 year old girl, made a suicide attempt (overdose) 4 days after discontinuing Adderall XR 30 mg. Patient 041-010 in study 302, an 8 year old girl, was hospitalized for suicidal threats and explosive temper one day after discontinuing Adderall XR 30 mg and beginning diazepam. Patient 102-021 in study 304, an adult who had discontinued Adderall XR for a hypomanic episode, developed suicidal ideation subsequently. Lastly, patient 455-001 in study 305, a 9 year old female, developed defiant behaviors after discontinuing Adderall XR.

There were 4 serious events in the “miscellaneous” category, all with open-label treatment (one “personality disorder” and 3 “depression” events). The three events coded as depression (in subject 007-026/study 302, a 9-year old female, and subject 320-009, study 305, 10 year old girl, and subject 027-002, study 315, 14 year old female) involved hospitalization for suicidal ideation, and perhaps could have been classified in the suicidal event category. Other serious adverse events, all with open label treatment, included 2 aggression events in boys, two suicidal events in adolescent females, and one event designated amphetamine psychosis in an adult male. One of the serious events in the aggression category (subject 010-006, study 302, 10 year old boy) involved not only aggression and threats to others but also threats of self harm.

Also with respect to classification, one event in study 305 described in the clinical narrative as leading to discontinuation was “aggression towards himself” (subject 276-003), but this was categorized as an aggression event.

#### **F. Atomoxetine (Strattera, NDA 21-411, Lilly)**

Atomoxetine is a specific norepinephrine reuptake inhibitor marketed for the indication of ADHD in both children and adults. A previous development program for the indication of depression in adults was not successful.

The current labeling for atomoxetine includes the following Warning regarding suicidal events in atomoxetine clinical trials:

##### **Suicidal Ideation**

STRATTERA increased the risk of suicidal ideation in short-term studies in children and adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of

STRATTERA in children and adolescents have revealed a greater risk of suicidal ideation early during treatment in those receiving STRATTERA. There were a total of 12 trials (11 in ADHD and 1 in enuresis) involving over 2200 patients (including 1357 patients receiving STRATTERA and 851 receiving placebo). The average risk of suicidal ideation in patients receiving STRATTERA was 0.4% (5/1357 patients), compared to none in placebo-treated patients. There was 1 suicide attempt among these approximately 2200 patients, occurring in a patient treated with STRATTERA. No suicides occurred in these trials. All events occurred in children 12 years of age or younger. All events occurred during the first month of treatment. It is unknown whether the risk of suicidal ideation in pediatric patients extends to longer-term use. A similar analysis in adult patients treated with STRATTERA for either ADHD or major depressive disorder (MDD) did not reveal an increased risk of suicidal ideation or behavior in association with the use of STRATTERA...

With respect to aggressive behaviors, the current labeling includes the following statement (under the Precautions section):

**Aggressive Behavior or Hostility** — Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no conclusive evidence that STRATTERA causes aggressive behavior or hostility, aggressive behavior or hostility was more frequently observed in clinical trials among children and adolescents treated with STRATTERA compared to placebo (overall risk ratio of 1.33 – not statistically significant). Patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

#### Lilly suicidal event analysis

The labeling cited above for suicidal ideation was based on an analysis by Lilly of suicidal events in atomoxetine randomized, double-blind trials, requested by FDA in December 2004, and completed and submitted by Lilly in September 2005. Briefly, their methods and findings were as follows. Adverse event preferred terms, verbatim terms and comment fields were searched for text strings that might represent suicidal behaviors or ideation. Two different sets of text string terms were used for these searches, one requested by FDA and one devised by Lilly. False positives returned by these searches were excluded by review, and the events were classified into one of several categories of self injury or suicidal ideation. Statistical testing was performed using the Mantel-Haenzel incidence difference test. The results for the pediatric and adult atomoxetine trials are shown in the table below. By the FDA criteria, there were a total of 6 events classified as suicidal behavior or ideation among atomoxetine treated pediatric patients (6/1357, 0.4%) versus no such events among 851 placebo-treated patients (p-value = 0.01). Of the six pediatric events, one involved suicidal behavior and 5 involved suicidal ideation.

Overall, there was not the same imbalance between drug and placebo in the adult trials that was observed in the pediatric trials. The events in adult trials included one adult completed suicide on placebo. By indication, only one event occurred in an adult ADHD trial (on placebo).

**Table F1. Lilly analysis of suicidal events in atomoxetine clinical trials**

Category of events	Pediatric studies		Adult studies	
	Atomoxetine (n = 1357)	Placebo (n = 851)	Atomoxetine (n = 1718)	Placebo (n = 1072)
Suicidal events, FDA definition	6 (0.4%)*	0	15 (0.9%)	10 (0.9%)
Suicidal events, Lilly definition	7 (0.5%)**	1 (0.1%)	11 (0.6%)	8 (0.7%)

\*p-value versus placebo = 0.01

\*\*p-value versus placebo = 0.07

#### Lilly analysis of hostility and aggression

In April 2005, Lilly submitted an analysis of hostility and aggression in their pediatric atomoxetine double blind clinical trials. As with the analysis described above, they searched their clinical trial preferred terms, verbatim terms and comments fields for a variety of text strings that possibly represented hostility or aggression. Events returned by the search were reviewed by two health care professionals blind to treatment, and were classified into one of 6 possible categories of hostility or aggression, or were excluded. This yielded the results displayed in the following table. The combined risk ratio for aggressive events (atomoxetine:placebo) was 1.33 (0.67-2.64).

**Table F2. Lilly analysis of aggression in atomoxetine pediatric clinical trials**

Category of events	Frequency in pediatric double blind trials		
	Atomoxetine (n = 1308)	Placebo (n = 806)	MPH active control (n = 472)
Aggression and hostility, Lilly definition	21 (1.6%)	9 (1.1%)	4 (0.8%)

#### Response to September 2005 Data Request

The following tables display the results of the requested search. There were a total of 18 randomized, double blind trials of atomoxetine in pediatric patients with ADHD, and 3 such trials in adults. The ADHD safety and efficacy trials contributing data are summarized in Appendix table F.

The next table shows the summary results for all ages combined.

**Table F3. Frequency of patients with psychiatric adverse events in adult and pediatric ADHD safety and efficacy trials (Lilly response to September 14, 2005 letter)**

Study design	Treatment	N	Patient years of exposure	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	1443	350.73	0	4	18
DB	Atomoxetine	2459	654.87	4	9	49
DB	Atomoxetine+Concerta	9	0.87	0	0	0
DB	Atomoxetine+Fluoxetine	114	11.92	0	2	0
DB	Fluoxetine	120	7.54	0	1	2
DB	Methylphenidate	515	69.21	0	1	7
Open	Atomoxetine*	5270	5095.27	12	44	198
Run-in	Atomoxetine	812	177.80	2	3	47

\*This total is for atomoxetine without other drugs; there were no events among the small numbers of patients who received open label atomoxetine with another drug

Limiting the data to pediatric patients yields the following new totals for atomoxetine and placebo.

**Table F4. Pediatric ADHD safety and efficacy trials: frequency of patients with adverse psychiatric events.**

Study design	Treatment	N	Patient years of exposure	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	1056	256.02	0	3	15
DB	Atomoxetine	1939	524.64	4	8	45
DB	Atomoxetine+Concerta	9	0.87	0	0	0
DB	Atomoxetine+Fluoxetine	114	11.92	0	2	0
DB	Fluoxetine	120	7.54	0	1	2
DB	Methylphenidate	515	69.21	0	1	7
Open	Atomoxetine	4669	4546.74	12	44	191
Run-in	Atomoxetine	812	177.80	2	3	47

Note that there were proportionally more aggression events during run-in treatment than during double blind treatment with atomoxetine. It will be seen that there is an imbalance in the numbers of patients with events in all three categories for double blind atomoxetine versus placebo, even after accounting for the approximately 2:1 ratio of patient-years of exposure. However, the imbalance for suicidal events is not as great as it was in Lilly's previous analysis of suicidal adverse events. The present results include some additional clinical trial data that was not part of Lilly's previous analyses. Relapse prevention trials were not included in Lilly's analyses, and removing these two trials (HFBE and LYAF) from the pool of trials yields the following totals, which are more comparable to the previous analyses by Lilly. For simplicity, only the double blind data are shown, since the other data are not affected by removing the relapse prevention trial data.

**Table F5. Pediatric ADHD safety and efficacy trials, omitting long term relapse prevention trials: frequency of patients with adverse psychiatric events.**

Study design	Treatment	N	Patient years of exposure	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	839	144.54	0	1	12
DB	Atomoxetine	1616	296.50	4	4	38

This subgrouping yields an incidence rate ratio for the pooled data on suicidal events of 1.9, with wide confidence limits (0.19-96, Stata 7.0). The incidence rate ratio for aggression events is 1.5 (c.i. 0.8-3.2), and due to an absence of events on placebo the ratio is undefined for psychosis/mania events, with a p-value of 0.2 for the comparison between drug and placebo.

Differences in the search strategies employed seem to account for some of the differences in the numbers of cases. In their submission dated 12-8-05, Lilly was able to reconcile the counts of cases between their own analyses of aggression and suicidal events and their response to FDA's September 2005 request. Lilly found that certain cases from their previous analyses had not been returned in the FDA-requested search, because (1) in response to the FDA request (unlike their previous analyses) they had not searched comments fields from the case report forms, and (2) in their previous searches they had used more inclusive text strings resulting in greater sensitivity. Additionally, Lilly had potential cases adjudicated by experts prior to analyzing the data, and this was not part of the present analysis.

In addition to the pediatric ADHD trials, there was one pediatric study (LYBH) in patients with enuresis, and the data from this trial are displayed below.

**Table F6. Frequency of patients with adverse events in enuresis trial LYBH**

Study design	Treatment	N	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	43	0	0	2
DB	Atomoxetine	44	0	0	0
Open	Atomoxetine	64	0	1	1

The sponsor also provided the corresponding data for the adult depression trials, which is summarized below. Psychosis/mania events were more frequent among atomoxetine treated patients, while suicidal and aggressive events were less frequent, proportional to exposure time.

**Table F7. Adult major depressive disorder safety and efficacy trials: frequency of patients with adverse psychiatric events.**

Study design	Treatment	N	Patient years of exposure	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	653	156.99	1	5	3
DB	Atomoxetine	1178	333.31	6	5	3
Open	Atomoxetine	42	12.11	0	0	0

With respect to events occurring after treatment discontinuation, the sponsor provided listings of such events, but these proved difficult to analyze because the listings were not organized according to indication or category of event. The events occurring after treatment were not included in the data shown above.

**G. Ritalin LA (NDA 21-284, Novartis)**

Ritalin LA is an extended release formulation of methylphenidate. There were 5 controlled trials and one open label trial in the Ritalin LA development program, as summarized in Appendix table G. All trials involved only pediatric subjects.

The next table displays the summary data on the psychiatric events of interest.

**Table G. Frequency of patients experiencing selected psychiatric events in Ritalin LA clinical safety and efficacy studies.**

Study design	Treatment	N	Person-yrs	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	259	11.31	0	1*	0
DB	Ritalin LA	383**	25.66	2	0	2
Open	Ritalin LA OL	125	25.95	0	1	0
DB	Concerta	89	2.82	0	0	0

\*One additional suicidal event occurred within 30 days of the end of treatment in a patient who had been randomized to placebo

\*\*includes single blind Ritalin LA exposures in Protocol 07

Narratives for patients with serious adverse events and trial discontinuations for adverse events were reviewed, disclosing one event which could arguably have been included in the category of suicidal events but apparently was not: in Protocol 07, patient 503/6, an 8-year old male receiving double blind Ritalin LA, was hospitalized for suicidal ideation. The event was coded as depression and counted in the category “miscellaneous.” Although the post-treatment suicidal event involving a placebo patient was designated serious, none of the events enumerated in the table above during study treatment were considered serious.

**H. Focalin (NDA 21-278) and Focalin XR (NDA 21-802) (Novartis)**

Focalin and Focalin XR are drug products with dextromethylphenidate (d-MPH) as the active ingredient. The XR product is an extended release formulation. In the following data presentations the two formulations will be combined and listed as d-methylphenidate (d-mph). The trials in the sponsor’s development program for both formulations are summarized in Appendix table H. All trials involved pediatric patients except for one placebo-controlled trial in adults (E2302) which included open label follow-up treatment (designated E2302E).

The table below summarizes the numbers of events in trials with d-MPH. There were no events of interest with placebo treatment. Note that Novartis apparently included 3 events occurring after discontinuation of open-label d-MPH treatment in these counts, which was not the intention. However, because data on which category the event was classified in was not always provided in the listing of events, making it difficult to match the counts of events with particular cases in the patient listings, it was decided to leave the events in the counts displayed below rather than to try to correct the totals.

**Table H1. Frequency of patients experiencing selected psychiatric events in Focalin and Focalin XR clinical safety and efficacy studies.**

Study design	Treatment	N	Person- yrs	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	468	53.24	0	0	0
DB	d-MPH*	588	64.75	4	0	1
Open	d-MPH*	740	362.09	3	1	13
DB	Concerta	164	5.89	1	0	0
DB	dl-MPH	46	3.59	0	0	0

\*Focalin and Focalin XR

Novartis’ analysis of these data showed that aggressive events were more frequent among males than females (data not shown).

The sponsor reported that in the clinical pharmacology studies there were no relevant psychiatric adverse events. One pediatric patient (97 M 05/2708) had a psychosis/mania event three weeks after open label treatment was discontinued (psychotic depression with homicidal ideation, requiring hospitalization). Also, there was one miscellaneous event with a serious outcome, patient 22-03 in study 97 M 04, but this patient’s event was also counted as psychosis/mania (see below).

The table below shows the data for the subgroup of trials involving only subjects of pediatric age.

**Table H2. Summary data from pediatric trials in the d-MPH development program**

Study design	Treatment	N	Person-yrs	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	415	48.47	0	0	0
DB	d-MPH*	420	49.73	1	0	0
Open	d-MPH*	570	302.87	2	1	11
DB	Concerta	164	5.89	1	0	0
DB	dl-MPH	46	3.59	0	0	0

\*Focalin and Focalin XR

Review of the narratives for patients with serious adverse events and trial discontinuations disclosed two events which arguably could have been included in the category of suicidal events, but were not. Both patients were treated with open label d-MPH in study 97 M 04. Patient 22-03, a 7 year old boy, was hospitalized after placing a belt around his neck and showing aggressiveness, and hallucinating. This patient was counted in the psychosis/mania category. Patient 23-31, a 12 year old boy, was hospitalized with psychotic depression for violent behavior and suicidal and homicidal thoughts; this event was counted under psychosis/mania and aggression.

## 5. CONCLUSIONS

A. There are factors that limit the utility of these clinical trial data for determining whether any of these drugs are associated with the selected psychiatric events. Some of these limitations apply whenever clinical trial data are aggregated for analysis. For one, there is the issue of whether adverse events are ascertained with the same level of sensitivity by different investigators, and in different trials. This can present challenges when making comparisons between trials and between development programs. Secondly, there is the issue of whether cases could have been misclassified. The data presented herein were based upon each sponsor's adverse event classifications, but the methods employed to produce these classifications varied across sponsors. Third, the statistical power of such safety analyses are always limited by the sample sizes of the trials considered.

In addition to these general limitations which apply to all such safety analyses, there are additional limitation specific to these data. First, as can be seen from the tables in the appendix, a large number of the controlled trials required subjects who were known to respond to stimulants, or who had no history of intolerance to stimulants. This tends to limit the external generalizability of safety data collected from samples of such subjects, especially when the data obtained from the subjects show relatively infrequent adverse events. Secondly, it will be seen that the duration of exposure in many of these trials was likely to have been insufficient for determination of infrequent adverse events; e.g., although over a thousand pediatric subjects received double-blind treatment in one set of clinical trials, the average duration of exposure to double-blind treatment was only 23 days. To a certain degree this can be (and was) mitigated by greater exposure time in open label trials, but open label data is of less inferential value than controlled data. The

exception to this was the development program for atomoxetine, which included over 500 person-years of double blind atomoxetine pediatric exposure.

B. Undertaking a more formal meta-analysis of the clinical trial data for these events would have presented challenges because of the sparse nature of the data; many trials had no events at all.

C. With respect to specific findings, suicidal events were more frequent with atomoxetine and modafinil treatment than with placebo. It should be noted that there were no completed suicides in ADHD trials with these drugs (one completed suicide was reported in a placebo patient in an atomoxetine trial for another indication). Aggressive events were more frequent with the methylphenidate transdermal patch, and to a lesser degree with atomoxetine, than with placebo. None of these imbalances in rates reached customary levels of statistical significance in this analysis, although Lilly's previous analysis of suicidal events with atomoxetine did show a statistically significant association, as was summarized above. For aggression events, there was little evidence in these trials that drug treatment reduced their frequency relative to placebo; only for modafinil was the event rate numerically lower than for placebo and this was not statistically significant.

D. With respect to psychosis and mania events, although the numbers of such events with drug treatment were small, the complete absence of such events with placebo treatment was notable. For 4028 pediatric ADHD patients in these trials, there were no such events in 425 person-years of aggregated placebo treatment. Statistically, observing no events in 425 person-years yields an upper one-sided 97.5% confidence limit to the "true" event rate of 0.9 per 100 person-years. (Similarly, there were no psychosis or mania events in these trials among 578 adult ADHD patients receiving placebo for a total exposure time of 111.5 person-years in the adult age group.) Psychosis/mania events occurred during double-blind treatment with every compound except Adderall XR (although there were psychosis/mania events with open label Adderall XR treatment). Furthermore, as noted above, some subjects in Phase I studies of these drugs experienced this type of event.

E. Patients and physicians should be aware of the possibility that these events, when they arise in the course of drug treatment of ADHD, may represent adverse reactions to drugs.

F. In terms of future clinical trial designs, it should be borne in mind that short-duration trials and trials which exclude subjects who are naïve to this class of drug, while they may be efficient for determining efficacy, have limitations for defining the safety profile of the drug.

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Appendix Table A. ADHD safety and efficacy studies with Concerta included in analysis

Protocol	No. of sites	Age range (yrs)	Duration (dys)	Dose (mg/day)	N			Population	Comments	Study completion date
					Drug	Placebo	Active control			
C 97 025	1	6-12	6 3 way Xover	18-54	68	69	69 MPH	MPH users	Included laboratory school	1998
C 98 003	1	6-12	7 3 way Xover	18-54	62	61	63 MPH	MPH users	Included laboratory school	1999
C 98 005	14	6-12	28	18-54	104	98	104 MPH	MPH users or previous study subjects	Open label run-in phase was designated Study C 98 007	1998
C 98 007	14	6-12	21	18-54	110	-	-	Naïve or using drugs other than MPH	Open label run in for Study C 98 005	1998
C 98 012	14	6-13	> 1 yr	18-54	436	-	-	Subjects in previous trials	Long term open label	2000
C 99 018	118	> 6 incl. adults	9 mos.	18-54	1088	-	-	Naïve or previously drug treated	Long term open label	2001
01 146	15	13-18	14	18-72	87	90	-	ADHD	Randomized withdrawal design following open label run-in. Also included open label extension after DB phase	2002
12 101	323	6-12	21	18-72	~890	-	~445 atomoxetine	Drug naïve patients allowed	Randomized, open label design	2003
C2000 045	11 in Europe	6-16	Up to 12 mos	18-54	105	-	-	MPH users	Long term open label	2003
CONCAN1	?	6-12	8 wks	18-54	~75	-	~75 MPH	ADHD	Randomized, open label	2005?
CONCAN2	?	6-13	6 mos.	18-54	109	-	-	CONCAN1 subjects	Open label extension	2004

Abbreviations: mph methylphenidate; Xover crossover

Appendix Table B. ADHD safety and efficacy trials with Metadate CD included in the analysis

Protocol	No. of sites	Age range (yrs)	Duration (dys)	Dose (mg/day)	N			Population	Comments	Study completion date
					Drug	Placebo	Active control			
CD 00600	10	6-12	7 (3-way Xover)	20-60	173	181	180 Concerta	Mph users	Laboratory classroom study	2002
MAI 100102	1	7-12	7 (2 period Xover)	20 or 40	25	25	25 Mph	Mph users	Laboratory classroom study	1998
MAI 100104	32	School age, >6	21	20-60	158	163	-	Mph users	Single blind placebo run-in and double blind placebo exposure was combined in sponsor's analysis	1999
MAI 100302	44 (AUS, CAN, & US)	6-12	21	20-60	139	46	133 Mph	Mph users		2003
CD00500	51	6-17	-	20-60	308	-	-	Mph users (59% of sample) or previously untreated ADHD	Open label	2001
MAI 100103	1	6-11	49	10-30	8	-	-	Previously untreated ADHD	Open label	1999

Abbreviations: mph methylphenidate; Xover crossover

Appendix Table C. ADHD safety and efficacy trials with methylphenidate transdermal system (MTS) included in the analysis

Protocol	No. of sites	Age range (yrs)	Duration (dys)	Dose (mg/day)	N			Population	Comments	Study completion date
					Drug	Placebo	Active control			
N17-002	1	6-9	7 (3-way Xover)	10 cm <sup>2</sup>	10	10	10 Mph	ADHD	Laboratory classroom	1999
N17-003	1	6-10	2 Xover	2.5-20 cm <sup>2</sup>	13	13	-	ADHD	Laboratory classroom	1999
N17-009	3	6-12	1	6.25-25 cm <sup>2</sup>	36	36	-	ADHD	Summer camp	2000
N17-015	1	6-12	1 (multiple Xover)	6.25-25 cm <sup>2</sup>	27	27	-	No history of adverse responses to mph	Summer camp	2001
SPD485201	6	6-12	35d Open label, then 7d 2-way Xover	12.5-37.5 cm <sup>2</sup>	80	79	-	ADHD and no comorbid disorders except ODD	Laboratory classroom	2005
N17-010	20	6-12	21	6.25-25 cm <sup>2</sup>	101	109	-	ADHD		2001
N17-018	21	6-12	28	6.25-50 cm <sup>2</sup>	106	105	-	ADHD with or without current drug treatment		2002
SPD485302	38	6-12	49	12.5-37.5 cm <sup>2</sup>	98	85	91 Concerta	Stimulant nonresponders excluded		2005
N17-011	Multi	6-12	90	6.25-25 cm <sup>2</sup>	118	-	-	ADHD	Open label only	2000
N17-013	Multi	6-12	Until NDA approved	6.25-37.5 cm <sup>2</sup>	20 ongoing	-	-	Responders to mph patch in previous protocols	Continued open label treatment for patients who had positive response	Ongoing, interim data June 2005

N17-021	Multi	6-12	32 mos.	6.25-50 cm <sup>2</sup>	191	-	-	Subjects from N17-018	Continued open label treatment	2004
SPD485-303	Multi	6-12	1 yr	12.5-37.5 cm <sup>2</sup>	288 (ongoi ng)	-	-	Subjects from SPD485- 102 and SPD485-302	Ongoing open label study	2006 projected. Interim data from June 2005

Abbreviations: mph methylphenidate; Xover crossover

Appendix Table D. ADHD safety and efficacy studies with modafinil included in the analysis

Protocol	No. of sites	Age range (yrs)	Duratio n	Dose (mg/ day)	N		Population	Comments	Study completion date
					Drug	Placebo			
205	6 (phase A) 7 (phase B)	Adults 18-57	6 wks	100, 200, 400 (fixed)	109 (74 phase A, 35 phase B)	75 (38 Phase A, 37 Phase B)	ADHD without psychiatric comorbidity	Included 8 week open label extension	2001
207	3	6-13	1 wk 4 way Xover	0, 100, 200, 300/400	46	44	ADHD	Included 8 wk open label extension	2000
213	28	6-13	4 wks	300 or 400	197	51	ADHD, either stimulant -naïve or -tolerant	Included 8 wk open label extension	2002
309	18	6-17	9 wk	170-425	131	67	ADHD without psychiatric comorbidity	Parallel group, 2:1 randomization	2004
310	17	6-17	9 wk	340 or 425 according to wt	125	64	ADHD without psychiatric comorbidity	At week 7 modafinil patients were randomized to either modafinil or pbo for final 2 wks	2004
311	24	6-17	9 wk	170-425	164	84	ADHD without psychiatric comorbidity		2004
113	1	6-13	2 wks + 2 single doses	340,425	24	-	ADHD not responding well to medication	Bioavailability assessment was main objective	2003
206	3	6-12	4 wks	100-400	20	-	ADHD without	Included optional 8 wk	2000

							psychiatric comorbidity	extension	
312	56	6-17	1 yr	170-425	536	-	Tolerated modafinil in a previous ADHD trial		ongoing

Appendix Table E. ADHD Safety and Efficacy Studies with Adderall XR included in the analysis

Protocol	No. of sites	Age range (yrs)	Duration (dys)	Dose (mg/day)	N			Population	Comments	Study completion date
					Drug	Pbo.	Active control			
201	4	6-12	1 wk X over (5 way)	Adderall 10, Adderall XR 10,20,30	50	49	-	Current users of Adderall or MPH	Laboratory school setting	1999
301	47	6-12	3 wks	10, 20, 30 (fixed)	10 mg 129; 20 mg 121; 30 mg 124	210	-	ADHD, known to be tolerant of stimulants		2000
302	49	6-12	24 mos.	10-30	568	-	-	Participants in previous trials	Open label, long term safety	2002
303	18	≥18	4 wks	20, 40, 60 (fixed)	191	64	-	Adults with ADHD and no history of intolerance to stimulants		2002
304	18	≥18	24 mos.	20, 40, or 60	223	-	-	Adults who participated in study 303	Open label, long term safety	2005
305	365	6-12	15 wks	10-40	2968	-	-	Responders to prior stimulant treatment	Open label safety and efficacy	2002
311	27	6-17	4 wks	10, 20, 30, 40 fixed dose	237	60	-	Oppositional defiant disorder (not ADHD)		2003
312	81 (U.S., Canada)	≥18	40 wks	10-60	725	-	-	Previously treated or naive		2005
314a	50	13-17	4 wks	10, 20, 30, 40 (fixed)	258	69	-	ADHD, no special requirements		2003
314b	32	13-17	6 mos.	10-60	138	-	-	Subjects in study 314a	Long term extension of 314a	2004

315	~50	13-17	24 mos.	10-60	255 planned	-	-	Subjects in study 314a	Long term extension of 314a, 314b	ongoing
316	1	19-25	3 wk Xover	20-50	19	15	8* Atomoxetine	ADHD, not naïve to medication	Driving simulator study. Data from atomoxetine phase of study not provided.	2004
404	10	6-12	18 dys	10-30	107	211	108 atomoxetine	ADHD, no history of failure on medication, no psychiatric comorbidity	Laboratory school setting; randomized, double blind, no placebo	2004

\*data not provided

Appendix Table F. ADHD safety and efficacy studies with atomoxetine included in the analysis

Protocol	No. of sites	Age range (yrs)	Duration (wks)	Dose (mg/day)	N			Population	Comments	Study completion date
					Drug	Placebo	Active control			
HFBD	9	7-12	9	2 mg/kg/d	65	62	20 Mph	ADHD, with or without prior stimulant tx		2000
HFBK	10	7-12	9	2 mg/kg/d	64	62	18 Mph	ADHD, with or without prior stimulant tx		1999
LYAA	17	≥18	10	60,90,120	141	139	-	Adult ADHD		2001
LYAC	13	8-17	8	1.2 or 1.8 mg/kg/d	213	84	-	ADHD		2000
LYAO	14	≥18	10	60,90,120	129	127	-	Adult ADHD		2001
LYAS	15	7-17.5	18	0.5,1,1.5 mg/kg/d	76	72	-	ADHD plus tic disorder		2003
LYAT	9	6-16	6	0.75-1.5 mg/kg/d	85	86	-	ADHD		2001

LYAW	11	8-12	7	0.8-1.8 mg/kg/d	101	52	-	ADHD		2002
LYAX	16	12-17	9	0.8-1.8 mg/kg/d	72	70	-	ADHD plus major depression	Included open label extension	2004
LYBG	12	6-12	8	0.8-1.8 mg/kg/d	133	64	-	ADHD		2002
LYBI	21	6-16	6	0.8-1.8 mg/kg/d	222	74	220 Concerta	ADHD	Included double blind continuation phase	2003
LYBP	14	8-17	12	0.8-1.8 mg/kg/d	87	89	-	ADHD plus anxiety disorder	Atomoxetine dosed either am or pm	2004
LYCC	14	6-12	6	0.8-1.4 mg/kg/d	195	93	-	ADHD per DSM-IV-TR		
HFBC	1	7-13	100 dys	10-90	29	-	-	ADHD	Open label	1998
HFBE	23	7-16	48 wks	5-90	184 OL 42 DB	23	44 Mph OL	ADHD	Relapse prevention design with open label tx followed by randomized withdrawal of active drug	2000
HFBF	24	≥6	96 wks	5-90	325	-	-	ADHD subjects from a previous atomoxetine trial	Open label	2001
LYAB	53	6-18	2 yrs	≤1.8 mg/kg/d	914	-	-	ADHD	Long term open label	2001
LYAF	33 International	6-15	78 wks	≤1.8 mg/kg/d	292	124	-	ADHD	Relapse prevention study. A total of 604 patients received open label atomoxetine during run-in	ongoing
LYAI	31	6-17	-	-	296	-	-	Subjects in previous atomoxetine trials	Long term open label	ongoing
LYAQ	21	6-17	6 wks	≤1.8 mg/kg/d	44 atomoxetine 120 Fluoxetine 44 placebo 114 atomoxetine+fluoxetine			ADHD plus anxiety or depressive disorder	Trial of combination therapy with fluoxetine, included open label and double blind	2001
LYAR	30	≥18	Open ended	Up to 120	383	-	-	Adult ADHD	Long term open label	ongoing
LYAU	1	6-13	6 wks, 2 way Xover	0.5 – 1.8 mg/kg/d	8	-	8 Mph	ADHD, right handed	Functional MRI study	2003

LYAV	2	6-14	6 wks, 2 wasy Xover	1.6 mg/kg/d	80	-	81 Mph	ADHD	Sleep study comparing effects of atomoxetine and methylphenidate	2002
LYBB	40	6-18	10 wks	1.8 mg/kg/d	357	-	-	ADHD	Open label	2001
LYBD	19 (Japan)	6-18	8 wks	1.8 mg/kg/d	37	-	-	ADHD		2003
LYBM	14	18-50	6 wks	80	218	-	-	Adult ADHD	Acute phase compared 40 mg BID to 80 mg QD. Included continuation phase with 160 mg/d dosing.	2003
LYBR	13 International	6-16	8 wks	0.8-1.8 mg/kg/d	164	-	166 Mph	ADHD	Randomized, double blind, without placebo	2004
LYBU	5	6-12	4 wks + 6 wks	1.4 mg/kg/d	Atomoxetine alone 12 Atomoxetine + Concerta 9			ADHD, with poor response to stimulants	Randomized, double blind comparison of atomoxetine plus placebo to atomoxetine plus Concerta. Included 6 wk extension phase	2005
LYBV	23	18-50	6 mos.	40-100	271	139	-	Adult ADHD with stable employment	Assessment of work productivity was primary endpoint. Included 4 mo. Extension	2005
LYCI	6	6-17	8 wk	1.2 mg/kg/d	62	-	-	ADHD with poor response to stimulant	Open label	2005

Appendix Table G. ADHD safety and efficacy trials with Ritalin LA included in the analysis

Protocol	No. of sites	Age range (yrs)	Duration (dys)	Dose (mg/day)	N			Population	Comments	Study completion date
					Drug	Placebo	Active control			
02*	2	6-12	1 day (5-way Xover)	17.5-25	34	34	-	Mph users	Laboratory classroom	1999
07	15 (U.S. and Canada)	6-12	14-28 single blind run-in, 14 DB	10-40	161 single blind, 66 double blind	71	-	Mph users or naïve		2000

US02		12-17	**	**	99	102	-	**	All females	**
US05	1	6-12	Single dose, 4-way Xover	20	36	36	36 Concerta	Mph users	Laboratory classroom	2002
US07	3	6-12	Single dose, 5-way Xover	20 and 40	53	53	53 Concerta (two doses)	Mph users	Laboratory classroom	2003
07 E1	**	<17	**	**	125	-	-	**	Open label	**

\*There were no events in Protocol 02. Data were not available by specific treatment, and so were not included in the pooled analysis.

\*\*information not available

#### Appendix Tables H. ADHD safety and efficacy trials with d-methylphenidate included in the analysis

##### Focalin XR

Protocol	No. of sites	Age range (yrs)	Duration (dys)	Dose (mg/day)	N			Population	Comments	Study completion date
					Drug	Placebo	Active control			
2301	12	6-17	49	5-30	53	47	-	Mph users or naïve		2004
2302	18	18-60	35	20,30,40 (fixed dose)	165	53	-	Adults with ADHD		2003
US08	3	6-12	6 (2-way Xover)	20	54	54	-	Mph users	Laboratory classroom setting	2004
2302E1	18	18-60	6 mos.	10-40	170	-	-	Adults with ADHD	Open label follow-up to study 2302	2004
US09	4	6-12	7 (2 way Xover)	20	68	68	-	Stable users of Mph	Laboratory classroom setting	2004
US12	*	6-12	*	20,30	84	83	83 Concerta	*		*
US13	*	6-12	*	20,30	82	81	81 Concerta	*	5-way Xover	*

\*information not available

### Focalin

Protocol	No. of sites	Age range (yrs)	Duration (dys)	Dose (mg/day)	N			Population	Comments	Study completion date
					Drug	Placebo	Active control			
97-M-02	12	6-17	28	5-20 d-mph; 10-40 mph	44	42	46 (mph)	ADHD		1999
97-M-03	7	6-17	42d open label; 14d DB; 44 wk open label	5-20	35	40	-	ADHD	Three phases: (1) 6-wk open label dose optimization; (2) 2-wk randomized withdrawal; (3) open label treatment	2000
97-M-04	8	6-17	1 yr	5-20	187	-	-	ADHD	Long term open label	2000
97-M-05	27 (U.S. and Canada)	6-17	6 mo	5-20	361	-	-	ADHD	Long term open label	2000
00-M-06	2	6-18	8 wk	2.5-30	22	-	-	ADHD	Open label pilot	2002
00-M-07	?	<i>Adult</i>	<i>12 wk</i>	<i>5-50</i>	<i>15</i>	-	-	<i>Adults with ADHD</i>	<i>Open label pilot, data not provided</i>	<i>?</i>

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