

**Rapporteur's
Public Assessment Report
for paediatric studies submitted in accordance
with Article 46 of Regulation (EC) No1901/2006, as
amended**

UK/W/010/pdWS/001

Strattera

Atomoxetine

Marketing Authorisation Holder: Eli Lilly and Co.

Rapporteur:	UK
Start of the procedure:	Day 0 – Start procedure: 1 July 2009
Date of this report:	6 September 2009
Deadline for Rapporteur's pdAR(Day 70):	Preliminary PdPAR: 9 September 2009
Deadline for MS comments:	23 September 2009
Day 90:	7th October 2009
Day 115:	2nd November 2009
Day 120:	7th November 2009

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Strattera
INN (or common name) of the active substance(s):	Atomoxetine hydrochloride
MAH:	Eli Lilly and co.
Currently approved Indication(s)	Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children aged 6 years and above and in adolescents in the United Kingdom on 27 May 2004.
Pharmaco-therapeutic group (ATC Code):	Centrally acting sympathomimetics (NO6B A09)
Pharmaceutical form(s) and strength(s):	5 mg, 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg capsules.

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EXECUTIVE SUMMARY

This is an assessment of data for atomoxetine, as part of the Article 46 EU work-sharing procedure. The UK is Rapporteur for this product; the initial assessment report (day 70) is due to be circulated to concerned Member States on 9th September 2009.

On 14 May 2009 the MAH submitted 7 completed paediatric studies for atomoxetine, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. A critical expert overview has not been provided. The submitted studies are for the treatment of children and adolescents with ADHD and comorbid conditions, including oppositional defiant disorder (ODD) and reading disorder. The MAH stated that the submitted paediatric studies do not influence the benefit risk for atomoxetine and that there is no consequential regulatory action.

Strattera (atomoxetine) capsules were first authorized for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children aged 6 years and above and in adolescents in the United Kingdom on 27 May 2004. Subsequent Mutual Recognition Procedures (MRP) with the UK as Reference Member State (RMS) have resulted in atomoxetine being authorised in the majority of EU countries for use in children and adolescents as part of a comprehensive treatment programme. The Marketing Authorisation (MA) is currently undergoing renewal through the MRP with the UK as RMS.

In the UK, atomoxetine is a Black Triangle drug (a new drug under the MHRA intensive monitoring scheme). Since the original approval there have been several serious safety issues including psychiatric ones (eg suicidality, psychosis), leading to regulatory action.

Clinical data submitted

Studies in ADHD included one dose finding study and two randomised controlled trials (RCTs). In addition, there were two randomised controlled trials undertaken in children with ADHD and co-morbid oppositional defiant disorder (ODD) and one study in children with ADHD and co-morbid reading disorder.

None of the submitted trials for ADHD and co-morbid conditions provided any robust evidence of efficacy for the treatment of either ODD or reading disorder with atomoxetine. In addition, the dose finding study and two RCTs for ADHD did not provide any findings that require changes to the product information. Overall, in all of the studies, atomoxetine was well tolerated; there were few serious adverse events reported.

Final Recommendations

Comments were received from France, Norway, Sweden and the Netherlands; who all agreed with the assessor's recommendations.

The assessor concluded that no changes to the SmPC or PIL were necessary and that no other regulatory action was required. The procedure was completed on 7th November 2009.

I. INTRODUCTION

On 14th May 2009, the MAH submitted 6 completed paediatric studies for atomoxetine, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. A critical expert overview has not been provided. The submitted studies are for the treatment of children and adolescents with ADHD and comorbid conditions including oppositional defiant disorder (ODD) and reading disorder.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for atomoxetine and that there is no consequential regulatory action.

Regulatory History

Strattera (atomoxetine) capsules were first authorized for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children aged 6 years and above and in adolescents in the United Kingdom on 27th May 2004. Subsequent Mutual Recognition Procedures (MRP) with the UK as Reference Member State (RMS) have resulted in atomoxetine being authorised in the majority of EU countries for use in children and adolescents as part of a comprehensive treatment programme, with a notation in the Summary of Product Characteristics (SPC) that in some cases it might be appropriate to continue treatment into adulthood. Diagnosis should be made according to DSM-IV criteria or ICD-10 guidelines. The current UK Summary of Product Characteristics (SPC) for atomoxetine states that ‘treatment must be initiated by or under the supervision of a physician with appropriate knowledge and experience in treating ADHD’. Atomoxetine can be administered as a single daily dose in the morning, with or without food, or as twice daily evenly divided doses if a satisfactory clinical response to a single daily dose is not achieved.

Over 5.5 million patients are estimated to have been treated with atomoxetine since the initial regulatory approval in the United States on 26th November 2002.

Eight dosage strengths (5 mg, 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, and 100 mg) have been approved, with the recent approval of 80 mg and 100mg on 05 June 2008 (in the UK). The Marketing Authorisation (MA) is currently undergoing renewal through the MRP with the UK as RMS. The double-blind phase of studies BZ-SD-LY15 (a) and BZ-MC-LYBX have already been submitted in the Strattera Wave 3 MRP submission; the safety data for these studies have therefore not been assessed as part of the Article 46 procedure.

Since the original approval the following safety issues have arisen:

- In 2005, an EMEA Article 31 referral procedure that reviewed suicidal and suicidal-related behaviours in children and adolescents treated with SSRIs and SNRIs including atomoxetine, resulted in the revision of the SPC to include a warning for hostility and emotional lability. A statement that atomoxetine is not indicated for the treatment of major depressive episodes and/or anxiety was also added. Also in 2006, clinical trial reported suicide-related events was included in Section 4.8 as an uncommon event in children and adolescents (incidence $\geq 0.1\%$ and $<1\%$); further revision of statements regarding suicidality has been made in 2008.

- In 2009, continued case reports of possible nervous-system and psychiatric adverse effects prompted a review of data from all sources, resulted in updated information on the risk of new-onset or worsening of serious psychiatric disorders, including psychotic reactions, hallucinations, mania, and agitation. Atomoxetine is associated with treatment-emergent psychotic or manic symptoms in children and adolescents without a history of such disorders.
- Other important safety issues associated with atomoxetine include seizures, hepatotoxicity and QT prolongation.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the studies

Atomoxetine capsules were used in all of the clinical studies.

II.2 Clinical aspects

II.2.1 Introduction

The MAH submitted 7 final study reports for the treatment of children and adolescents with ADHD, ADHD and comorbid conditions including oppositional defiant disorder (ODD) and reading disorder: These are listed below:

Study B4Z-KL-LYEC - Randomized, Open-Label Assessment of Response to Various Doses of Atomoxetine Hydrochloride in Korean Paediatric Outpatients with Attention-Deficit/Hyperactivity Disorder.

Study B4Z-XM-LYDM- A Randomized Double Blind, Placebo Controlled Clinical Trial of Efficacy and Safety of Atomoxetine up to 12weeks in Newly Diagnosed Children and Adolescents Outpatients with Attention Deficit/Hyperactivity Disorder.

Study BZ-SD-LY15 (a) A Randomized, Double Blind, Placebo Controlled Study of the Broader Efficacy of Atomoxetine Hydrochloride in the Treatment of Attention-Deficit/Hyperactivity Disorder in Swedish Children and Adolescents

Study B4Z-MC-LYBX - A Randomized, Double-Blind Comparison of Atomoxetine Hydrochloride and Placebo in Child and Adolescent Outpatients with Attention-Deficit/Hyperactivity Disorder and Comorbid Oppositional Defiant Disorder.

B4Z-MC-LYBX - This was the open-label phase of the above study.

Study B4Z-IT-LYCY- An Italian Randomized, Double-blind Placebo Controlled Study of the Efficacy of Atomoxetine Hydrochloride in the Treatment of Children and Adolescents with Attention-Deficit/Hyperactivity Disorder and Comorbid Oppositional Defiant disorder

Study B4Z-MC-LYCK- A Randomized, Double-Blind, Crossover Comparison of Atomoxetine Hydrochloride and Placebo in Child Outpatients with Attention-Deficit/Hyperactivity Disorder, Reading Disorder, or Comorbid Attention-Deficit/Hyperactivity Disorder and Reading Disorder

Attention-Deficit/Hyperactivity Disorder (ADHD)

ADHD is a heterogeneous behavioural syndrome defined as a “persistent pattern of inattention or hyperactivity—impulsivity that is more frequently displayed and more severe than is typically observed in individuals at a comparable level of development.” It is the most commonly diagnosed psychiatric disorder in children, affecting about 3 to 5% of children globally with symptoms starting before seven years of age. ADHD is generally a chronic disorder with 30 to 50% of those individuals diagnosed in childhood continuing to have symptoms into adulthood. As they mature, adolescents and adults with ADHD are likely to develop coping mechanisms to compensate for their impairment. Though previously regarded as a childhood diagnosis, ADHD can continue throughout adulthood. Four percent of American adults are estimated to live with ADHD. ADHD is diagnosed twice as frequently in boys as in girls, though studies suggest this discrepancy may be due to subjective bias. Common comorbid conditions include oppositional defiant disorder (ODD), conduct disorder, learning difficulties, depression, substance misuse and epilepsy.

The updated National Institute for Health and Clinical Excellence (NICE) Guidelines for ADHD (September 2008) recommend that the diagnosis should only be made by a specialist psychiatrist, paediatrician or other healthcare professional with training and expertise in the diagnosis of ADHD.

For a diagnosis of ADHD, symptoms of hyperactivity/impulsivity and/or inattention should:

- meet the diagnostic criteria in DSM-IV or ICD-10 (hyperkinetic disorder) **and**
- be associated with at least moderate psychological, social and/or educational or occupational impairment based on interview and/or direct observation in multiple settings, **and**
- be pervasive, occurring in two or more important settings including social, familial, educational and/or occupational settings.

ADHD management usually involves some combination of medications, behaviour modifications, lifestyle changes, or counselling. The NICE guideline recommends that in school-age children and young people with severe ADHD, drug treatment should be offered as the first-line treatment. Parents should also be offered a group-based parent-training/education programme. Drug treatment for children and young people with ADHD should always form part of a comprehensive treatment plan that includes psychological, behavioural and educational advice and interventions. Methylphenidate is usually the first line drug of choice. Others include: dexamphetamine, atomoxetine, tricyclic antidepressants and clonidine.

The NICE guideline recommends that atomoxetine (or methylphenidate) should be the first-line choices for medication treatment of school-age children and young people with severe ADHD when tics, Tourette’s syndrome, anxiety disorder, stimulant misuse or risk of stimulant diversion are present. It also recommends that atomoxetine should be used if methylphenidate has been tried and has been ineffective at the maximum tolerated dose, or the child or young person is intolerant to low or moderate doses of methylphenidate.

Oppositional defiant disorder (ODD)

Oppositional defiant disorder (ODD) is a recurrent pattern of negativistic, defiant, disobedient, and hostile behaviour toward authority figures that persists for at least 6 months. Behaviours included in the definition include the following: losing one's temper; arguing with adults; actively defying requests; refusing to follow rules; deliberately annoying other people; blaming others for one's own mistakes or misbehaviour; and being touchy, easily annoyed or angered, resentful, spiteful, or vindictive. The base prevalence rates for oppositional defiant disorder (ODD) range from 1-16%, but most surveys estimate it to be 6-10% in surveys of nonclinical, non-referred samples of parents' reports. Before puberty, the condition is more common in boys; after puberty, it is almost exclusively identified in boys, and whether the criteria are applicable to girls has been discussed. The disorder usually manifests by age 8 years. ODD and other conduct problems are common reasons for referrals to outpatient and inpatient mental health settings for children, accounting for at least half of all referrals.

The diagnosis of ODD is complicated by relatively high rates of comorbid, disruptive, behaviour disorders. Some symptoms of ADHD) and conduct disorder overlap. Researchers have postulated that, in some children, ODD may be the developmental precursor of conduct disorder. Comorbidity of ODD with ADHD has been reported to occur in 50-65% of affected children. The presence of ODD together with ADHD is a serious clinical problem. Children with ADHD combined with ODD tend to have more severe ADHD symptoms, peer problems, and family distress compared with children with ADHD alone. However, few rigorous, adequately designed studies of pharmacologic treatments for ODD have been reported, although data from recent preliminary studies suggest that medications may be of benefit.

In some children, ODD commonly occurs in conjunction with anxiety disorders and depressive disorders. Cross-sectional surveys have revealed the comorbidity of ODD with an affective disorder in about 35% of cases, with rates of comorbidity increasing with patient age. High rates of comorbidity are also found among ODDs, learning disorders, and academic difficulties. Given these findings, children with significant oppositional and defiant behaviours often require multidisciplinary assessment and may need components of mental health care, case management, and educational intervention to improve.

Pharmacological properties

Unlike all other currently approved medicinal products to treat ADHD, atomoxetine is not a stimulant. It is a potent, selective and highly specific inhibitor of the presynaptic norepinephrine transporter (NET). It has minimal affinity for either the serotonin or dopamine transporters, or for other neurotransmitter receptors. Specific inhibition of the NET is believed to be the mechanism for the efficacy of atomoxetine in ADHD. Following oral administration of atomoxetine it is rapidly and almost completely absorbed resulting in maximal plasma concentrations after 1 to 2 hours. Metabolism is rapid and primarily by aromatic ring hydroxylation, aliphatic oxidation and N- demethylation to phase I metabolites (4-hydroxyatomoxetine, desmethyatomoxetine and

2-hydroxymethyl-atomoxetine). CYP2D6 is the major enzyme involved in the aromatic hydroxylation to the major metabolite 4-hydroxyatomoxetine, which undergoes further metabolism resulting in the formation of the primary ultimate metabolite of atomoxetine,

4-hydroxyatomoxetine-*O*-glucuronide. This conjugated metabolite is subsequently eliminated in the urine and the mean elimination half life is about 3.6 hours in extensive metabolisers and

21 hours in poor metabolisers. Atomoxetine does not cause clinically significant inhibition or induction of CYP1A2, CYP3A, CYP2D6 or CYP2C9.

The pharmacokinetics of atomoxetine are linear over the range of doses studied. In the paediatric population pharmacokinetic analysis, body weight had a significant effect on atomoxetine pharmacokinetics and therefore a weight-based dose regimen is authorised.

II.2.2 Submitted clinical studies

➤ Description

Study B4Z-KL-LYEC - Randomized, Open-Label Assessment of Response to Various Doses of Atomoxetine Hydrochloride in Korean Paediatric Outpatients with Attention-Deficit/Hyperactivity Disorder.

Objectives: The primary objective of this study was to assess graphically the monotonic ordering of response to three different doses of atomoxetine hydrochloride in Korean paediatric outpatients aged 6 to 18 years with ADHD, as measured by reduction from baseline to endpoint in Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) total score. The ADHD Rating Scale-IV is a validated instrument that includes 18 items, both used for diagnosing ADHD in children and adolescents and for assessing treatment response.

The secondary objectives of the study were as follows:

- To assess the efficacy of each dose in reducing the severity of ADHD symptoms, as measured by reduction from baseline to endpoint in Clinical Global Impression-ADHD-Severity (CGI-ADHDS) score.
- To assess the efficacy of each dose in reducing the severity of ADHD symptoms, as measured by Clinical Global Impression-ADHD-Improvement (CGI-ADHD-I) score at endpoint.
- To assess the safety and tolerability of atomoxetine at each dosage.

Study Design: This study was a Phase 3b multicenter, randomized, parallel, open-label trial assessing the monotonic ordering of response to three different doses of atomoxetine in 150 Korean paediatric outpatients aged 6 to 18 years with Attention-Deficit/Hyperactivity Disorder.

Diagnosis and Main Criteria for Inclusion: All patients enrolled in the study were children or adolescents of Korean origin, aged 6 to 18 years, with a diagnosis of ADHD, as determined by the Investigator according to the DSM-IV-TR disease diagnostic criteria. Criteria for enrolment included a symptom severity threshold of 1.5 standard deviations above age and gender norms on the ADHDRS-IV-Parent:Inv as well as a CGI-ADHD-S score ≥ 4 at Visits 1 and 2.

Study Drug, Dose, and Mode of Administration:

Arm 1: atomoxetine 0.2 mg/kg/day, given orally as a divided dose for 6 weeks.

Arm 2: atomoxetine 0.5 mg/kg/day, given orally as a divided dose for 6 weeks. .

Arm 3: atomoxetine 0.5 mg/kg/day for ~7 days, then atomoxetine 0.8 mg/kg/day for ~7 days and then atomoxetine 1.2 mg/kg/day for ~28 days, all given orally as a divided dose.

Variables:

Efficacy: Assessment of ADHD symptom response by comparing reduction from baseline to endpoint in ADHDRS-IV-Parent: Inv total score. Secondary efficacy variables included the CGI-ADHD-S and score and the CGI-ADHD-I score.

Safety: Assessment of adverse events (AEs), including serious adverse events (SAEs); vital signs; and weight.

Statistical Evaluation Methods:

Efficacy: The primary objective of this study was to assess graphically the monotonic ordering of response to three different doses of atomoxetine. Primary efficacy analysis was an intent-to-treat (ITT) analysis. All randomized patients with both a baseline and at least one postbaseline ADHDRS-IV-Parent:Inv total score and CGI-ADHD-S score were included. The primary summary statistic used to assess dose response was the treatment group least squares mean overall change from baseline to LOCF endpoint in ADHDRS-IV-Parent:Inv total score. This was calculated from an ANCOVA model which included terms for baseline ADHDRS-IV-Parent:Inv total score, treatment group and investigator. Secondary analyses examined change from baseline to endpoint CGI-S and CGI-I scores.

➤ **Results**

Efficacy

There was a monotonic ordering of dose response for atomoxetine prescribed at 0.2 mg/kg/day (n = 51), 0.5 mg/kg/day (n = 51), and 1.2 mg/kg/day (n = 51) in the improvement of ADHD symptoms in Korean children and adolescents following 6 weeks of treatment, as assessed by change from baseline to endpoint in Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv) total scores.

Additional sensitivity analyses provided strong supportive evidence of the monotonic dose response relationship observed in the primary efficacy analysis. Secondary efficacy analyses demonstrated that atomoxetine at 1.2 mg/kg/day provided clinically meaningful and statistically significant improvements in ADHD symptoms compared with atomoxetine at a sub-therapeutic dose of 0.2mg/kg/day.

Safety

There were no unexpected safety findings in this study. Atomoxetine at 1.2 mg/kg/day (58.3%) demonstrated a greater rate of treatment-emergent adverse events than atomoxetine at 0.2 mg/kg/day (29.4%). Among treatment-emergent adverse events, there was a statistically significant difference overall between the three treatment arms in terms of somnolence. The most frequently reported TEAEs among patients in the as-treated population were decreased appetite, anorexia, upper abdominal pain, nasopharyngitis, and irritability.

Assessor's comments

This trial did not provide any new information requiring changes to the product information.

➤ **Description**

Study B4Z-XM-LYDM-A Randomized Double Blind, Placebo Controlled Clinical Trial of Efficacy and Safety of Atomoxetine up to 12weeks in Newly Diagnosed Children and Adolescents Outpatients with Attention Deficit/Hyperactivity Disorder.

This multicenter Spanish study was undertaken between 2005-8.

Objectives:

The primary objective of the study was to test the hypothesis that efficacy was superior in atomoxetine-treated patients compared to those on placebo, as assessed by ADHDRS-IV-Parent:Inv total score after 12 weeks of treatment among newly diagnosed cases of ADHD outpatients.

Secondary objectives:

- To evaluate the efficacy of atomoxetine compared to placebo, using ADHDRS-IV-Parent:Inv total score after 9, 6 and 4 weeks of treatment and its change from week 6 to week 12 of treatment.
- To evaluate the efficacy of atomoxetine compared to placebo using:
 - Clinical Global Impression-Severity-ADHD (CGI-ADHD-S) during double blind period.
 - Conner's Parent Rating Scale-Revised (CPRS-R:S) during double blind period.
 - Child Health and Illness Profile (CHIP) for the quality of life for each age group (6-11, 11 and up) up 12 weeks.
- To assess long-term efficacy with atomoxetine in the patients that qualified and chose to enter the open label period measured by the change from baseline in total score from the ADHDRS-IV-Parent:Inv, CGI-ADHD-S and CPRS-R:S during the open label phase of study.
- To assess safety and tolerability among this patient population during double blind and open label phase of study.
- To describe comorbidity among this patient population with Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADSPL).

Study Design: This was a double blind, placebo-controlled clinical trial in 153 children with newly diagnosed ADHD. Patients were randomized in a 2:1 ratio of atomoxetine 1.2mg/kg to placebo for 12 weeks. There was an open-label extension treatment with atomoxetine for up to 1 year.

Diagnosis and Main Criteria for Inclusion: Child or adolescent patients ≥ 6 and < 16 years old at Visit 1, newly diagnosed of Attention-Deficit/Hyperactivity Disorder (ADHD) confirmed by the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV-TRTM) and drug naïve before Visit 1.

The Primary objective: was to test the hypothesis that efficacy was superior in atomoxetine-treated patients compared to those on placebo, as assessed by ADHDRS-IV-Parent:Inv total score after 12 weeks of treatment among newly diagnosed cases of ADHD in outpatients.

Secondary Objectives

If atomoxetine was assessed to be statistically significantly superior to placebo based on the primary analyses, then ADHDRS-IV-Parent:Inv total score were tested using a stepdown strategy after 9, 6, and 4 weeks of treatment and change from week 6 to week 12 of treatment. Testing stopped when a measure failed to show statistical significance favouring atomoxetine ($p \geq 0.05$).

Additional secondary objectives of study LYDM were to assess the following:

- Clinical Global Impression-Severity-ADHD (CGI-ADHD-S) during double blind period.
- Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) during double blind period.
- Long-term efficacy with atomoxetine in the patients that qualified and chose to enter the open label period measured by the change from baseline in the total score from the ADHDRS-IVParent: Inv, CGI-ADHD-S and CPRS-R:S during the open label phase of study.
- Quality of life assessed by Child Health and Illness Profile (CHIP) for each age group (6-11, 11 and up) up 12 weeks.
- To assess safety and tolerability among this patient population during double blind and open label phase of study.
- To describe baseline comorbidity among this patient population with Kiddie Schedule for
- Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL).

Primary efficacy analysis: This was undertaken by repeated measures analysis of least square means across treatment at the final week of the double-blind phase (Visit 7), including ADHDRS-IV-Parent:Inv total score as response variable, treatment, investigator, visit, and treatment by visit interaction as fixed factors, and patient (within-treatment) as random factor, with baseline score and baseline by visit interaction as covariates. The Repeated Measures (MMRM) technique was done: at weeks 9, 6, and 4 and change from week 6 to week 12 of treatment. Testing was stopped when a measure failed to show statistical significance favouring atomoxetine ($p \geq 0.05$).

➤ **Results:**

- A total of 151 patients were randomized and treated; 149 evaluated as ITT population in the double blind period (98.7%), and 140 continued to the open-label extension period (92.7%).

Efficacy

- The primary endpoint was confirmed: atomoxetine was statistically superior to placebo in the reduction of the ADHDRS-IV-Parent:Inv total score after 12 weeks of double blind treatment (adjusted difference of -7.91; 95%CI between -11.04 and -4.77; which meant more than 30% of total score decrease). This difference was also considered to be clinically significant. That difference was also significant after 9 weeks ($p < 0.001$), 6 weeks ($p < 0.001$) and 4 weeks of treatment ($p < 0.001$), and for the change from week 6 to week 12 ($p = 0.013$).
- Atomoxetine was also superior to placebo in the inattention subscale, in the hyperactivity/impulsivity subscale, and in the number of ADHD symptoms improvement at all assessed weeks.
- Atomoxetine was also superior to placebo in the CPRS-R: S total score scale, in the cognitive problems subscale, in the hyperactivity subscale, in the ADHD Index; and in the CGI-ADHD score at all assessed weeks; but it was not statistically different to placebo in the oppositional subscale.
- Atomoxetine improved HRQoL with respect to placebo in the risk avoidance and achievement domains as assessed by parents and in the risk avoidance domain by patients.

Open-label period

Atomoxetine reduced ADHDRS-IV-Parent:Inv total score in 17.8 from baseline to the last open-label visit, which meant a 45% decrease. Secondary efficacy measures also showed a sustained improvement.

Safety

Decreased appetite and headache were the most frequently reported treatment emergent adverse events regardless their relationship to the study drug. Only one patient experienced a serious adverse event that was thought to be attributable to atomoxetine; this occurred during the open label phase.

Assessor's comments

Psychological support was not provided in this study- this should be part of a comprehensive treatment plan. The long term (only 1 year) data are encouraging.

Overall, this trial did not provide any new information requiring changes to the product information.

➤ Description

Study BZ-SD-LY15 (a) A Randomized, Double Blind, Placebo Controlled Study of the Broader Efficacy of Atomoxetine Hydrochloride in the Treatment of Attention-Deficit/Hyperactivity Disorder in Swedish Children and Adolescents

This was a multicentre, 10-week double blind randomized placebo control clinical trial, undertaken between 2005-6 in approximately 100 paediatric patients aged 7 to 15 years with ADHD.

The Primary objective: To test the hypothesis that atomoxetine and psychoeducation given for 10 weeks is superior to placebo and psychoeducation in improving overall functioning of patients, age 7-15 years, with Attention-Deficit/Hyperactivity Disorder (ADHD), as measured by the mean change in the total score of the Child Health and Illness Profile-Child Edition-Parent form (CHIP-CE-Parent form) domain Achievement. The CHIP-CE is a validated questionnaire that measures quality of life, that includes the following domains: achievement, satisfaction, comfort, resilience and risk avoidance. The achievement domain assesses academic performance by asking how the child has performed academically.

Secondary objectives: To compare the effects of atomoxetine and psychoeducation with those of placebo and psychoeducation at 10 weeks in patients with ADHD using the CHIP-CE-Parent form domains Satisfaction, Comfort, Resilience, and Risk avoidance, all CHIP-CE-Parent form subdomains, the CHIP-CE-Parent form total score, the Attention-Deficit/Hyperactivity Disorder - Rating Scale (ADHD-RS) total score regarding core ADHD symptoms, the Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity (CGI-S) and -Improvement (CGI- I) regarding severity of illness and improvement, the "I Think I Am" ("Jag tycker jag är") tool regarding self-perception, the Appraisal of Stress in Child-Rearing (ASCR) regarding family stress, and the Family Burden of Illness Module (FBIM; also known as the Family Strain Index [FSI]) regarding family burden of illness.

Diagnosis and Main Criteria for Inclusion: Patients had to meet the criteria for ADHD of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV™) as well as a symptom severity threshold of 1.5 standard deviations above age and sex norms for their diagnostic subtype on the Attention-Deficit/Hyperactivity Disorder Rating Scale-Parent Version (ADHDRS-IV-Parent); had to be between 7 and 15 years of age; had **not** to be previously treated with central stimulants. The diagnosis of ADHD and comorbid diagnoses were established by using the K-SADS diagnostic interview.

Study period I

Details regarding study period I were not provided.

Study Periods II-III

Study Period II was a double-blind placebo controlled period of 10 weeks, followed by Study Period III, an optional open-label extension period of 39 weeks on active treatment). In parallel, the parents of both study groups received a psychoeducation program for 4 weeks. Atomoxetine, 0.5 mg/kg/day (patients weighing <70 kg) or 40 mg/day (patients weighing 70 kg or more) during the first week of Study Periods II and III. Thereafter (Study Periods II and III), the dose was to be titrated upwards to a maintenance dose of 1.2 mg/kg/day (patients weighing <70 kg) or 80 mg/day (patients weighing 70 kg or more).

Primary Efficacy Variables: The primary efficacy variable was the mean score on the Achievement domain of the CHIP-CE. The primary efficacy analysis was a last observation carried forward (LOCF) analysis of covariance (ANCOVA) on the change from baseline (scores obtained at Visit 2) to Visit 7 (end of Study Period II) CHIP-CE-Parent form, achievement domain.

Secondary Efficacy Variables: CHIP-CE-Parent form (other domains, subdomains, and total score), ADHD-RS total and sub scores, CGI-S and CGI- I, the “I Think I Am” (“Jag tycker jag är”) tool, and the Appraisals of Stress in Child-Rearing (ASCR).

➤ **Results**

Study Period II

- A total of 102 patients entered the study and 99 patients were randomized, 49 to treatment with atomoxetine and 50 to treatment with placebo. Since none of the patients terminated the study prematurely, all randomized patients completed the full course of the 10-week double-blind treatment period (Study Period II). There were no relevant differences between treatments for any of the baseline characteristics.
- Atomoxetine was statistically significantly superior over placebo in the primary variable of the change from baseline to endpoint in the CHIP-CE Parent form Achievement domain (LS mean change for atomoxetine 6.9, for placebo 3.0, treatment difference 3.9, $p=0.010$).
- Overall, secondary efficacy variables showed that most patients improved during Study Period II, with more pronounced improvements seen in the atomoxetine group.
- The high effect size on ADHD core symptoms reported may be attributed to the exclusion of patients previously treated with stimulants, the long study duration of 10 weeks, and the mandatory 4 psychoeducative group sessions for the parents (by increasing treatment compliance and decreasing premature discontinuations).
- During Study Period III and in both treatment groups based on the treatment previously received in Study Period II, further improvements were observed for most efficacy variables. Such improvements were more pronounced in the placebo group, i.e., for patients who switched from placebo in Period II to atomoxetine in Period III.

Safety

The results of the double blind phase had been assessed in previous applications. The safety profile for atomoxetine seen in this study was reported to be in line with its safety profile in previous studies. During the open label phase there were no unexpected or serious safety findings; atomoxetine appeared to be well tolerated.

Assessor's comments

This study design was robust, as it included psychological support, rather than treatment with medication alone.

This trial did not provide any new information requiring changes to the product information.

➤ Description

Study B4Z-MC-LYBX -A Randomized, Double-Blind Comparison of Atomoxetine Hydrochloride and Placebo in Child and Adolescent Outpatients with Attention-Deficit/Hyperactivity Disorder and Comorbid Oppositional Defiant Disorder.

Method

The primary objective of this study was to test the hypothesis that atomoxetine hydrochloride (hereafter referred to as atomoxetine), given at a dose of 1.2 mg/kg/day (once daily) for approximately 8 weeks, is superior to placebo in the treatment of children and adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD) and comorbid Oppositional Defiant Disorder (ODD). Symptom change was measured by mean reduction in ODD symptoms on the investigator-rated Oppositional subscale of the Swanson, Nolan and Pelham Rating Scale-Revised (SNAP-IV).

The secondary objectives of the study were as follows:

- To test the hypothesis that atomoxetine given at a dose of 1.2 mg/kg/day (once daily) is superior to placebo in reducing symptoms of ADHD as measured by mean change in the investigator-rated SNAP-IV ADHD subscales.
- To compare the efficacy of atomoxetine given at a dose of 2.4 mg/kg/day with atomoxetine given at a dose of 1.2 mg/kg/day in reducing symptoms of ODD (in patients with peak plasma atomoxetine concentrations <800 ng/mL during once daily dosing) as measured by mean change in ratings on the Oppositional subscale of the SNAP-IV.
- To compare the efficacy of atomoxetine given at a dose of 2.4 mg/kg/day with atomoxetine given at a dose of 1.2 mg/kg/day in reducing symptoms of ADHD (in patients with peak plasma atomoxetine concentrations <800 ng/mL during once-daily dosing) as measured by mean change in ratings on the ADHD subscale of the SNAP-IV.
- To test the hypothesis that atomoxetine is superior to placebo in reducing symptoms of ADHD and ODD as measured by mean change in ratings on the Clinical Global Impressions-Severity (CGI-S).
- To test the hypothesis that atomoxetine is superior to placebo in improving psychosocial functioning as measured by the Total score on the Attention-Deficit/Hyperactivity Disorder Impact Module (AIM).
- To investigate the role of environmental stress, as measured by the Social Readjustment Rating Scale (SRRS), in the exacerbation of ODD symptoms
- To assess the safety and tolerability of atomoxetine compared with placebo as assessed by adverse events (AEs) elicited during open-ended questioning.

Study Design: This was a multicentre, randomized, double-blind, placebo-controlled, parallel group comparison of outpatients with ADHD and comorbid ODD. Patients were aged 6 to 12 years old.

Diagnosis and Main Criteria for Inclusion: Patients who were at least 6 years of age and not more than 12 years of age at Visit 1 and met the disease diagnostic criteria for ADHD and comorbid ODD as determined by a physician investigator's clinical assessment using the DSM-IV criteria for ADHD and criteria for ODD, the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version structured interview (K-SADS-PL), and the SNAP-IV ADHD subscale score, the CGI-S score, and the SNAP-IV ODD subscale score.

The SNAP-IV is a 26-item scale that includes 1 item for each of the 18 symptoms contained in the DSM-IV diagnosis of ADHD and 1 item for each of the 8 symptoms contained in the DSM-IV diagnosis of ODD. Each item is scored on a 0 to 3 scale (0- "not at all," 1- "just a little," 2 - "pretty much," 3 -"very much"). The SNAP-IV has been validated and normalised in a sample of school-aged children from the United States and yields scores in 3 domains: inattention, hyperactivity/impulsivity, and oppositional.

Study LYBX consisted of 5 study periods:

Study Period I: Screening, assessment, and washout.

Study Period II: (primary objective placebo-controlled phase). This was a randomized, double-blind, placebo controlled, 8-week treatment comparison of atomoxetine (1.2 mg/kg/day) or placebo in a 2:1 ratio in 220 patients.

Study Period III, Dose Comparison Phase: This was a randomized, double-blind, acute dose comparison: Atomoxetine-treated patients who did not achieve a peak plasma concentration of at least 800 ng/mL and did not demonstrate adequate ODD symptom reduction during Study Period II were re-randomized in a 1:1 ratio to either a higher dose (2.4 mg/kg/day) or the same dose (1.2 mg/kg/day) of continued atomoxetine treatment for approximately 4 weeks. All other Study Period II completers were eligible to continue into Study Period III and were not re-randomized. Study Period II atomoxetine remitter patients continued at 1.2 mg/kg/day and Study Period II placebo patients were titrated to 1.2 mg/kg/day of atomoxetine.

Study Period IV and Study Period V were open-label extension phases. Additionally, Study Period VI was later added to extend treatment for patients in 4 countries where atomoxetine was not yet commercially available at completion of Study Period V.

The primary efficacy variable was the SNAP-IV ODD total score. The primary efficacy analysis was a repeated measures analysis repeated measures analysis (MMRM) during study period 2. Additionally there was a comparison of least-square means across treatment at the final week of study period 2 (visit 5). The independent effects in the model included the investigator, treatment, visit, and treatment-by-visit interaction. Baseline was defined as scores obtained for visit 1 or visit 2.

Secondary efficacy variables Several scales were used as secondary outcome measures:

The Clinical Global Impressions-Severity Scale (CGI-S), as used in this study, measured the severity of the patient's ADHD and comorbid ODD symptoms; the Clinical Global Impressions-Improvement Scale (CGI-I) measured the improvement (or worsening) of ADHD and ODD symptoms; the Conners' Global Index-Parent Version (CGI-P) is a 10- item rating scale completed by the parent(s) to assess problem behaviours.; the Social Readjustment Rating Scale was completed by the parent(s) and provided an indication of the level of stress in the family unit; the ADHD Impact Module (AIM) is a specific ADHD health outcomes instrument that has been developed recently but has not been extensively validated (J. Landgraf, MS, Lilly Research Laboratories, unpublished internal report, 1999). It was designed to measure the impact of ADHD on the emotional and social well-being of the child and family.

➤ **Results**

(figure 1):

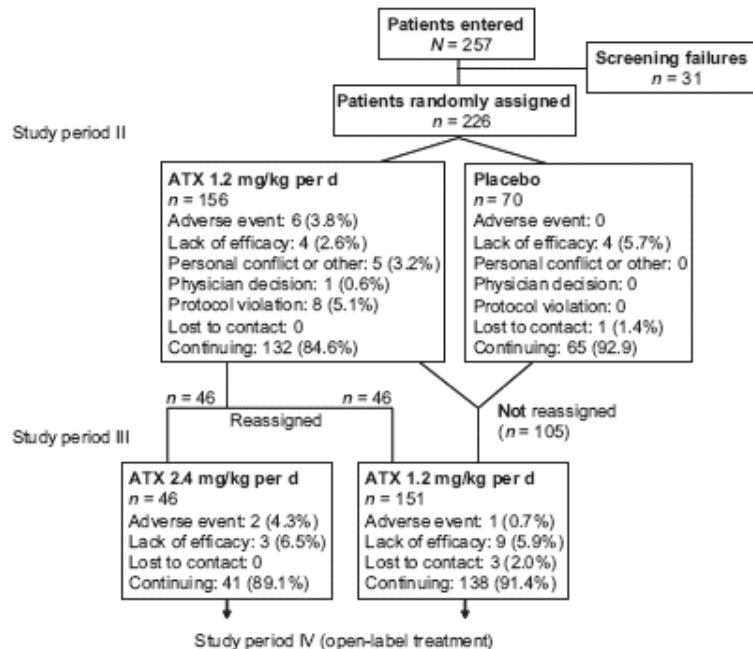


FIGURE 1
Patient flow diagram. ATX indicates atomoxetine.

Overall, discontinuations during Study Period II were low (n=29; 12.8%) and were similar between treatment groups with no statistically significant differences. In the atomoxetine treatment group the most common reason for discontinuation was protocol violation; (n=8; 5.1%). Six (3.8%) patients discontinued due to a treatment-emergent adverse event (TEAE). In the placebo treatment group the most common reason for discontinuation was lack of efficacy, patient and physician perception (n=2; 2.9%). No placebo-treated patients discontinued due to an AE.

Efficacy Results, Study Period II (Primary Objective Phase- atomoxetine 1.2 mg/kg/day vs placebo for 8 weeks in 226 patients)

Primary Efficacy Outcome: Results of the repeated measures analysis (MMRM) of the SNAP-IV ODD subscale score demonstrated that overall treatment effect of atomoxetine was statistically significantly greater than that of placebo (p=.01). However, for each visit MMRM analysis of least square means showed that there was a statistically significantly greater ODD symptom improvement on the SNAP-IV ODD subscale in the atomoxetine treatment group compared to the placebo treatment group at Visit 3 (2 wks, p=0.003) and Visit 4 (5 wks p=0.043), but not at Visit 5 (8 wks, p=0.209).

Secondary Efficacy Outcomes: All SNAP-IV subscale scores (18 ADHD subtype and combined items and 8 ODD items) were analyzed by last –observation- carried- forward (LOCF) mean change from baseline to endpoint. Statistically significantly greater ADHD symptom improvement was demonstrated in the atomoxetine treatment group compared to the placebo treatment group on all 3 ADHD subtypes: Combined (p<.001), Inattentive Subtype (p<.001), and Hyperactive/Impulsive (p=.003). The ODD Subscales score did not demonstrate statistically significant separation between treatment groups when analyzed by LOCF mean change from baseline. Improvement in ODD symptoms in both groups was indicated by increases in mean change scores from baseline to endpoint.

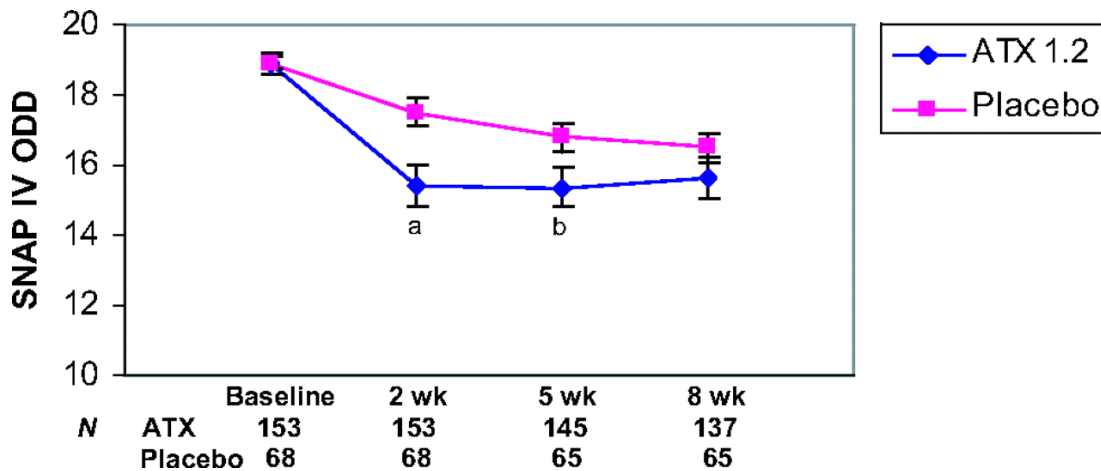
Atomoxetine treated patients also demonstrated a statistically significant greater responder rate of 20.5%; $p=.011$ (reduction of 1 SD of SNAP IV ODD subscale and an improvement of 1 point on the CGI-AHDH/ODD-S) compared with the placebo treated patients who demonstrated a response rate of 7.1%. Additionally, atomoxetine treated patients also demonstrated a statistically significant greater remitter rate of 11.5%; $p=.041$ (score of <9 on the SNAP IV ODD subscale and a score of 1 or 2 on the CGI-I (ADHD/ODD)) compared with the placebo treated patients who demonstrated a remitter rate of 2.9%.

Other secondary outcomes demonstrating statistically significantly greater symptom improvement in the atomoxetine treatment group compared with the placebo treatment were the CGI-I [ADHD/ODD] score, the CGI-S [ADHD/ODD] score, the CGI-PE total score and the Restless/Impulsive subscale score ($p<.001$). Results of the CGI-PY Emotional Lability Subscore indicated symptom improvement with a mean score increase in both treatment groups but did not reach a statistically significant difference. The Social Readjustment Scale (SRRS) score did not show statistically significant separation.

Efficacy Results, Study Period III (figures 2 and 3)

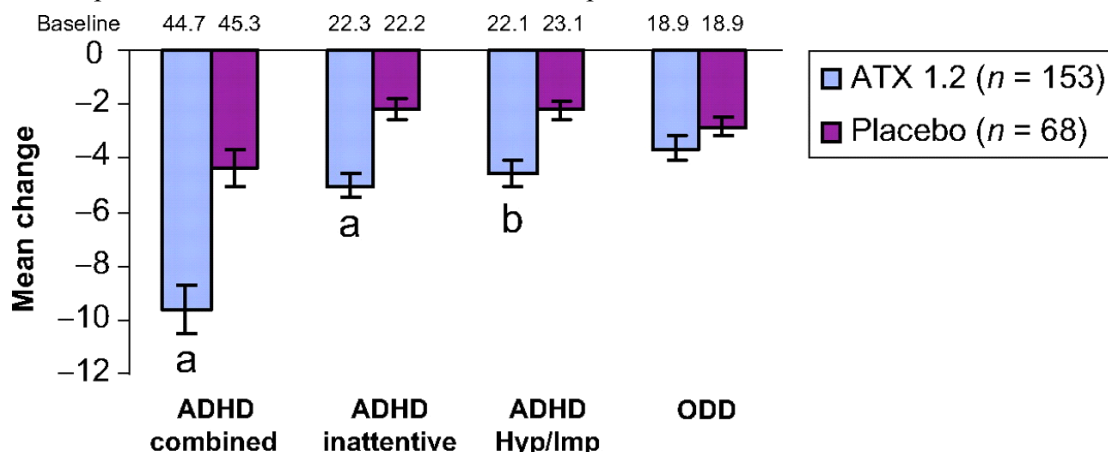
Results of dose comparison outcomes in non-remitters for LOCF mean change from baseline to endpoint did not reveal statistically significant differences between treatment groups in Study Period III on the primary SNAP-IV ODD subscale score or any of the SNAP-IV ADHD subtype subscale scores. However, both atomoxetine treatment groups (1.2 mg/kg/day and 2.4 mg/kg/day) demonstrated a mean score decrease at endpoint on all subscales of the SNAP-IV, suggesting symptom improvement in both ADHD and ODD symptoms. Also noted was the greater severity at baseline of Study Period III (Visit 5) of ODD symptoms. The trend of continued ADHD and ODD symptom improvement in both atomoxetine treatment groups was also seen on all of the other secondary outcomes (CGI-I, CGI-S, CGI-P evening, and the SRRS) during Study Period III. However, none of the secondary outcomes demonstrated statistically significant separation between the high- and low-dose atomoxetine-treated patients.

FIGURE 2 Repeated-measures analysis of the SNAP-IV ODD subscale. ^a $P < .01$ for atomoxetine 1.2mg/kg versus placebo; ^b $P < .05$ for atomoxetine 1.2 versus placebo. The overall treatment effect was significant: $P = .01$. ATX indicates atomoxetine.



Bangs, M. E. et al. Pediatrics 2008;121:e314-e320

FIGURE 3 Secondary SNAP-IV analyses (last observation carried forward). ^a $P < .001$ for atomoxetine versus placebo; ^b $P < .01$ for atomoxetine versus placebo. ATX indicates atomoxetine.



Bangs, M. E. et al. Pediatrics 2008;121:e314-e320

Safety Results, Study Period II

The results of the double blind phase had been assessed in previous applications. There were no deaths in this study and few serious ADRs. Overall, atomoxetine appeared to be well tolerated during this study.

➤ Description

B4Z-MC-LYBX

This was the open-label phase that was conducted at 17 study centres in 8 countries between 2004-8. It consisted of Study Period IV (Visits 7-13- 173 patients) and Study Periods V-VI (Visits 14-25). These extension phases allowed eligible patients to receive continued atomoxetine treatment for up to 4 years duration.

Overall, data suggested that atomoxetine was effective in reducing the signs and symptoms of ADHD and co-morbid ADHD. Atomoxetine appeared to be well tolerated; there were no unexpected safety signals during this period.

Assessor's comments

This trial did not include any adolescents with ADHD/ODD, which is disappointing. In addition, psychological support is not provided-this should be part of ADHD/ODD management; it should therefore be included (or at least discussed) in the study protocol.

Although atomoxetine treatment demonstrated a statistically significantly greater overall treatment effect compared with placebo treatment on the primary efficacy analysis of the SNAP-IV ODD subscale score in patients with ADHD and comorbid ODD, comparison of least square means across treatment groups at the final week of Study Period II (Visit 5-(8 weeks)) did not demonstrate a statistically significant difference. The clinical significance of the treatment effect is difficult to assess.

In addition, there was no evidence of any difference in efficacy between the higher and lower dosage groups in study period III.

Therefore, whilst the results of this study are encouraging, there is no robust evidence of efficacy for atomoxetine for the treatment of ODD symptoms in children and adolescents with (ADHD) and comorbid Oppositional Defiant Disorder (ODD).

➤ **Description**

Study B4Z-IT-LYCY-An Italian Randomized, Double-blind Placebo Controlled Study of the Efficacy of Atomoxetine Hydrochloride in the Treatment of Children and Adolescents with Attention-Deficit/Hyperactivity Disorder and Comorbid Oppositional Defiant Disorder

This study was conducted at 13 study centres in Italy in 2004-8.

Objectives: The primary objective of this study was to test the hypothesis that atomoxetine was superior to placebo in improving ADHD symptoms after 8 weeks of double-blind treatment on fixed dosage of atomoxetine (1.2 mg/kg/day, once daily) in paediatric outpatients with ADHD and ODD.

The secondary objectives of the study were to assess whether:

- Atomoxetine was superior to placebo in improving symptoms of ADHD as measured by mean change in Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S);
- Parent support induced a different response on ADHD symptoms in respect to ODD symptoms evaluated by the mean change in the ADHD subscale and in the Oppositional subscale of the SNAP-IV respectively;
- Atomoxetine was superior to placebo in reducing symptoms of Oppositional Defiant Disorders as measured by mean change in ODD symptoms on the investigator-rated Oppositional subscale of the SNAP-IV;
- Atomoxetine was superior to placebo in improving mood of children and adolescents with ADHD as measured by the anxiety/depression scales [Screen for Child Anxiety Related Emotional Disorders (SCARED), and Children's Depression Rating Scale-Revised (CDRS-R)];
- Atomoxetine was superior to placebo in improving problem behaviours related to ADHD (even in the school setting) as measured by Conners' Parent and Teacher Rating Scale-Revised: Short Form (CPRS-R:S and CTRS-R:S);
- Atomoxetine had a superior effect in comparison to placebo on the emotional and social well being of the child and the family evaluated by the total score on the Child Health and Illness Profile – Child Edition (CHIP-CE).

Other secondary objectives were: to assess whether the changes observed over 8 weeks were maintained over the open-label long-term phase of the study; to evaluate the long-term tolerability and safety of atomoxetine as assessed by adverse events (AEs) elicited during open ended questioning.

Study Design: This was a phase IIIb multicenter, randomized, placebo controlled, trial in paediatric patients, aged 6 years to 15 years with ADHD and ODD.

The entire study included four study periods:

- a) **Study period I** (screening phase): this was a screening and assessment/evaluation period, ranging from 3 to 28 days, to ensure eligibility for the study, and was started after parent's consent was obtained.
- b) **Study period II** (open-label, parent support phase): during this 6-week phase, the investigators provided a standardized management of parental support. Parents received weekly series of advice on the management of the behavioural problems of their children from qualified psychologists or child psychiatrists, based on standardized procedures. Response criteria were defined as an improvement in CGI-S score of 2 or more from baseline and at least a 30% decrease from baseline in the 18 items of the ADHD subscale score of investigator-rated SNAP-IV. Only patients who did not respond to the parent support phase were randomized to the study period III.

- c) **Study period III** (randomized, double blind, placebo-controlled phase). This was an 8-week period of double blind treatment in which 137 patients were randomly assigned to treatment with atomoxetine or placebo in a ratio of 3:1. Patients randomized to atomoxetine were titrated, in 7 days, from 0.5 mg/kg/day (allowed range from 0.5 to 0.8 mg/kg/day) to the target dose of 1.2 mg/kg/day (allowed range from 1.0 to 1.4 mg/kg/day), to be administered for the first 8 weeks of the study once daily in the morning.
- d) Study period IV (long-term, open-label extension phase). This was an optional, open-label, long-term extension phase for patients who had completed study period III, in which all patients had the choice to receive open label atomoxetine treatment for a long-term period until the drug became commercially available.

Main Criteria for Inclusion:

Child or adolescent male or female outpatients, aged 6 to 15 years meeting DSM-IV diagnostic criteria for ADHD (any subtype) and ODD and score at least 1.5 standard deviations above the age norm for their diagnostic ADHD-RS subtype at both Visit 1 and 2. A SNAP-IV ODD subscale score of at least 15 at both Visit 1 and Visit 2.

Primary Efficacy Variable: This was the ADHD subscale score of the SNAP-IV (i.e. based on the 18 Inattention, and Hyperactivity/Impulsivity items).

Secondary Efficacy Variables:

- ODD subscale score of the SNAP-IV;
- Other ADHD subscales (inattention and hyperactivity/impulsivity) of the SNAP-IV;
- CGI-S;
- Children's Depression Rating Scale-Revised (CDRS-R) and the Screen for Child Anxiety Related Emotional Disorders (SCARED) - Parent Version;
- Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) and the Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R:S);
- Child Health and Illness Profile -Child Edition (CHIP-CE) total score, domains, and subscores.

➤ **Results:**

137 patients were randomized and analyzed for safety and efficacy. A total of 132 patients (atomoxetine: 100; placebo: 32) entered the Study period IV (long-term, open-label extension phase with atomoxetine).

The two study groups were homogeneous for demographic data, DSM-IV ADHD diagnosis and anxiety/affective disorders at baseline.

Previous psychotherapy (of any type) was documented in 18 patients (17.1%) in the atomoxetine group and 6 (18.8%) in the placebo group, while 21 (20.0%) and 4 (12.5%) patients, respectively, received previous drug therapy. The mean starting dose of atomoxetine was 0.61 ± 0.08 mg/kg/day (range 0.44-0.80) and was titrated to 1.10 ± 0.13 mg/kg/day (range 0.85-1.33) at the end of the randomized phase of the study.

Primary Efficacy Analysis:

A non-clinically significant decrease in all SNAP-IV subscales scores was observed during the parent support phase. The mean score (\pm standard deviation) for the ADHD subscale (i.e. the sum of the 18 items for inattention and hyperactivity/impulsivity) was 43.3 ± 6.6 at the start and 42.1 ± 6.9 at the end of this phase, 21.9 ± 3.3 and 21.3 ± 3.6 for the inattention subscore, 21.4 ± 4.2 and 20.8 ± 4.3 for the hyperactivity/impulsivity subscore, and 18.1 ± 2.5 and 17.2 ± 3.3 for the ODD subscore.

During the randomized phase of the study, the mean changes (\pm standard deviation) from visit 8 to the last visit in this phase (i.e. visit 14 LOCF) in the ADHD subscale were -8.1 ± 9.2 and -2.0 ± 4.7 , respectively in the atomoxetine and in the placebo group ($p < 0.001$ between groups). A significantly stronger decrease of mean scores for all SNAP-IV subscales from visit 8 to the last visit was observed in the atomoxetine group, compared to placebo ($p < 0.01$) (table 2). However, the mean change in the SNAP-IV ODD subscale for atomoxetine relative to placebo was only -2.7 vs -2.2 , which is considered not to be clinically significant.

Table 2. Results of the SNAP-IV subscales scores during the randomized double blind phase (values are means \pm standard deviation)

	Atomoxetine (n = 105)			Placebo (n = 32)		
	Visit 8	Last Visit	Change from Visit 8	Visit 8	Last Visit	Change from Visit 8
ADHD subscale	42.7 \pm 6.2	34.6 \pm 10.2	-8.1 \pm 9.2**	41.5 \pm 6.9	39.5 \pm 8.7	-2.0 \pm 4.7
Inattention	21.6 \pm 3.2	17.5 \pm 5.2	-4.2 \pm 4.9**	21.2 \pm 4.3	20.4 \pm 4.8	-0.8 \pm 3.0
Hyperactivity/impulsivity	21.1 \pm 4.2	17.1 \pm 6.0	-3.9 \pm 5.0*	20.3 \pm 3.6	19.0 \pm 5.2	-1.3 \pm 2.8
ODD	17.2 \pm 3.0	14.5 \pm 4.8	-2.7 \pm 4.1*	17.5 \pm 3.8	17.2 \pm 3.9	-2.2 \pm 3.9

* $p < 0.01$, ** $p < 0.001$ between groups based on least square means from the ANCOVA model

In the open-label extension phase, patients previously on atomoxetine experienced a further decrease in the ADHD subscale. The mean change from Visit 14 to Visit 24/Last visit (i.e. visit 24 or earlier in the discontinued patients) in patients previously on atomoxetine was -9.0 (95% CI: -11.4 to -6.6), while a similar decrease was also observed in those previously on placebo (mean change: -8.9 ; 95% CI: -13.7 to -4.2). A similar pattern was also observed in the inattention, hyperactivity/impulsivity, and ODD subscores.

Secondary Efficacy Endpoints:

The mean CGI-ADHD-S score did not change from the start (mean score: 5.2) to the end (mean score: 5.1) of the parent support phase. A small decrease in the CGI-ADHD-S occurred in the double blind phase; this continued during the open-label extension phase. There were also non-significant changes in the other secondary variables: CDRS-R and SCARED, PRS-R:S and CTRS-R:S: Statistically significant differences vs. placebo were found in all subscales of the CPRS-R:S and in the oppositional subscale of the CTRS-R:S. In addition, there were statistically different changes in the mean changes of CHIP-CE total score (3.6 with atomoxetine vs 1.2 with placebo ($p = 0.071$ between groups)). The comparisons between groups showed statistically significant differences, in favour of atomoxetine, for the risk avoidance domain ($p = 0.013$), and for the emotional comfort ($p = 0.007$) and the individual risk avoidance ($p = 0.007$) subscores.

Safety

There were no unexpected adverse events Overall, atomoxetine appeared to be well tolerated, with no new safety signal detected.

Assessor's comments

It is not clear when patients had stopped receiving previous medication, as no washout phase is mentioned. It is also of note that the atomoxetine group had a higher rate of previous medication than the treatment group (21 (20.0%) vs 4 (12.5%) patients); this may have affected the results.

There appeared to be a statistically and clinically significantly greater overall treatment effect of atomoxetine compared with placebo treatment on the primary efficacy analysis of the SNAP-ADHD subscale score in patients with ADHD and comorbid ODD. However, there was not a clinically significant difference between atomoxetine and placebo on ODD symptoms as measured by mean change in ODD symptoms on the investigator-rated Oppositional subscale of the SNAP-IV.

➤ Description

Study B4Z-MC-LYCK- A Randomized, Double-Blind, Crossover Comparison of Atomoxetine Hydrochloride and Placebo in Child Outpatients with Attention-Deficit/Hyperactivity Disorder, Reading Disorder, or Comorbid Attention-Deficit/Hyperactivity Disorder and Reading Disorder

This study was a randomized, double-blind crossover study comparing atomoxetine with placebo in paediatric outpatients conducted at 7 study centres in 2 countries between 2005-7.

Primary Objective: The primary objective of this study was to test the hypothesis that acute treatment with atomoxetine hydrochloride for approximately 4 weeks provided superior efficacy compared with placebo in patients with Attention-Deficit/Hyperactivity Disorder-Combined Type (ADHD-C), Reading Disorder (RD) without ADHD, and comorbid ADHD-C and RD (ADHD-C+RD) as measured by improvement in speed of inhibition as shown by a statistically significantly shorter Stop Signal Reaction Time (SSRT) as derived from the SSRT Paradigm. The stop-signal reaction-time (SSRT) task measures inhibition of a response that has already been initiated, that is, the ability to stop. Human subjects classified as "impulsive," for example, those with attention deficit and hyperactivity disorder, are slower to respond to the stop signal.

Secondary Objectives: The secondary objectives of this study were as follows:

- In a subset of patients aged 10 years and older, compare performance of ADHD-C, RD, and ADHD-C+RD groups with normal controls and untreated RD controls on SSRT and a phonological reading task.
- Compare performance of ADHD-C, RD, and ADHD-C+RD patients with normal controls and untreated RD controls on SSRT and a lexical decision reading task.
- Establish the specificity of atomoxetine effect upon SSRT and the phonological and lexical decision tasks. The study assessed the effect of atomoxetine on:
 - a) Only inhibitory function (SSRT) task
 - b) Only influence on the reading tasks (phonological and lexical)
 - c) Influences in both types of tasks (SSRT and phonological task; and SSRT and lexical task)If c) was true, it may have been concluded that atomoxetine has general cognitive effects not specific for inhibition.
- Determine the effect of atomoxetine compared with placebo upon impulsivity (effect upon the trade-off between accuracy and speed of processing) in SSRT and a phonological and a lexical decision task in the following groups of patients: ADHD-C, RD, and ADHD-C+RD.
- Determine the effect of atomoxetine compared with placebo upon working memory as assessed by the Corsi Block Tapping Test (CBTT) in the following groups of patients: ADHD-C, RD, and ADHD-C+RD.
- Test the hypothesis that atomoxetine is superior to placebo in reducing symptoms of ADHD, as measured by mean change in the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv) in the following groups of patients: ADHD-C and ADHD-C+RD.
- Compare the clinical effect of atomoxetine with placebo in reducing symptoms of ADHD, using the Clinical Global Impression-Attention-Deficit/Hyperactivity Disorder-Improvement Scale (CGI-ADHD-I) and Clinical Global Impression-Attention-Deficit/Hyperactivity Disorder-Severity Scale (CGI-ADHD-S) in the following groups of patients: ADHD-C and ADHD-C+RD.
- Compare the safety and tolerability of atomoxetine with placebo as assessed by adverse events (AEs) elicited during open-ended questioning.

Study Design

Study LYCK was a randomized, double-blind crossover study comparing atomoxetine with placebo in paediatric outpatients. Study Period I (Visits 1 and 2) consisted of an initial screening and washout period. In Study Period II (Visits 3 through 5), eligible patients were randomly assigned to receive either atomoxetine (an initial dose of 0.6 mg/kg daily for 7 days followed by 1.2 mg/kg daily for 21 days) or placebo in a 1:1 ratio in a double-blind manner. for approximately 4 weeks. Patients then underwent a 2-week washout

period after which they were crossed over to receive the alternate treatment (atomoxetine or placebo) at Visit 4 for an additional 4 weeks. Study Period III (Visits 6 through 12) was open label and provided continued treatment with atomoxetine for approximately 11 months for patients in 1 study country where atomoxetine was not commercially available at the end of Study Period II.

Diagnosis and Main Criteria for Inclusion: Patients between the ages of 8 to 12 years of age at the time of enrolment and who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition™ (DSM-IV™) for ADHD-C and/or RD.

Primary Efficacy Variable:

This was the patient SSRT score as estimated using the SSRT Paradigm task assessed for all randomly assigned patients with ADHD-C, RD, or comorbid ADHD-C and RD, and who received at least 1 dose of study medication. Efficacy was assessed using a repeated measures analysis of SSRT scores conducted at post treatment Visit 3 and Visit 5 during the acute crossover treatment phase (Study Period II). Baseline was defined as the SSRT value obtained at visit 2.

Secondary Efficacy Variables:

These were as follows: patient SSRT scores in compliant patients (Per-Protocol Sample) with ADHD-C, RD, or comorbid ADHD-C and RD, and who received study medication. Patient SSRT scores by age compared to untreated RD and normal controls.

➤ **Results**

Efficacy

Patients receiving atomoxetine demonstrated lower SSRT scores overall compared to patients receiving placebo. Patients in the ADHD-C and ADHD-C+RD arms demonstrated lower (better) mean SSRT scores with atomoxetine treatment compared with placebo treatment. Patients in the RD study arm demonstrated a higher (worse) mean SSRT score with atomoxetine treatment compared with placebo.

Safety

No deaths or other SAEs were reported during the study. There was a statistically significant increased frequency of abdominal pain (p=.046), fatigue (p=.011), and nausea (p=.20) observed in patients taking atomoxetine compared to patients taking placebo during study period II. There were no unexpected safety signals; atomoxetine was well tolerated during this study.

Assessor's comments

There was no robust evidence provided that atomoxetine improved the speed of inhibition as shown by a statistically significantly shorter Stop Signal Reaction Time (SSRT) for patients with ADHD and reading disorder, or patients with reading disorder alone. It is of concern that this drug might be used in otherwise normal children with reading disorder.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

The submitted studies provide useful data regarding the use of atomoxetine for ADHD and other co-morbid conditions: oppositional defiant disorder and reading disorder. Some of the study designs were disappointing as they did not include the use of non-drug methods in the treatment of ADHD, which are part of a comprehensive treatment plan. There were no significant safety findings in the submitted data. In conclusion, the submitted data do not warrant any new indications, or other changes to the product information.

Recommendation

No changes to the product information or other regulatory action are recommended.

Fulfilled –

No further action required.

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable.

V. COMMENTS FROM MEMBER STATES

Comments were received from France, Norway, Sweden and the Netherlands; who all agreed with the assessor's recommendations.

VI. RAPPORTEUR'S FINAL RECOMMENDATIONS

The assessor concluded that no changes to the SmPC or PIL were necessary and that no other regulatory action was required. The procedure was completed on 7th November 2009.