131

Sok Central

Till: Ulla Liminga; Salmonson Tomas; Bergman Bo; Melander Hans; Abedi Alenoosh; Kroon Cecilia

Ämne: VB: Prozac 20mg Capsules (PL 006/0195) and Prozac Oral Liquid 20mg/5ml (PL0006/0272) ? Mutual Recognition (UK/H/636/01, 03) / EMEA/H/A-6(12)/671 submission to fulfil specific obligations

Bifogade filer: 005 Cover Letter Paed Ind Var FUM TADsJr Protocol 29Sept.doc; DRAFT Addendum HCLU to TADS Jr. Protocol_9_29_06_TO EU.doc; DRAFT TADS Jr. Protocol_9_27_06.doc; Ref Tanner-jm-87.pdf; Ref Tanner-jm-85.pdf

1994-0110, Fontex® Basal, 20 mg, Kapsel, hård, EMEA/H/A-11/403eller? EMEA/H/A-6(12)671, 113:2005/32197

1994-0112, Fontex®, 4 mg/ml, Oral lösning, EMEA/H/A-11/403, 113:2005/32197

Svar på frågor -> ~~IA~~ VB -> 0

/Anna

Från: Carly Anderson [mailto:ANDERSON_CARLY@LILLY.COM]
Skickat: den 5 oktober 2006 11:29
Till: christa.wirthumer-hoche@ages.at; kristof.liszka@ages.at; hilde.trouillard@health.fgov.be; Alban.dhanani@afssaps.sante.fr; s.winterscheid@bfarm.de; rieh@bfarm.de; kkehagia@eof.gr; Cathy.hempenstall@imb.ie; g.conti@aifa.gov.it; s.petraglia@aifa.gov.it; Jacqueline.genoux-hames@ms.etat.lu; rita.rigueiro@infarmed.pt; afernandez@agemed.es; mgarciav@agemed.es; mmartinez@agemed.es; Abedi Alenoosh; Sok Central
Kopia: saadia.sharief@mhra.gsi.gov.uk; Martina.Riegl@mhra.gsi.gov.uk
Ämne: Prozac 20mg Capsules (PL 006/0195) and Prozac Oral Liquid 20mg/5ml (PL0006/0272) ? Mutual Recognition (UK/H/636/01, 03) / EMEA/H/A-6(12)/671 submission to fulfil specific obligations

Please see the attached letter, draft protocols and references.

Many thanks,
Carly Anderson

Carly ANDERSON PhD
Regulatory Scientist - European Regulatory Affairs

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Dr Martina Riegl
Medicines and Healthcare products Regulatory Agency
Market Towers
1 Nine Elms Lane
Vauxhall
London SW8 5NQ

29th September 2006

Dear Dr Riegl,

Re: Fluoxetine capsules and oral solution UK/H/636/01,03/II/02
EMEA/H/A-6(12)/671 submission to fulfil specific obligations for Module 5

On June 1 2006, a positive opinion was adopted by the CHMP for the use of fluoxetine in the EU for the treatment of "major depressive episodes" in children aged 8 to 17 years. At the time of the opinion, Lilly agreed to undertake a number of specific obligations to address issues raised by the CHMP (refer to Lilly's letter to Dr D. Brasseur, EMEA, dated 31 May 2006).

To fulfil part of the obligation for Module 5, please find the following documents attached:

1. **Draft** protocol of the National Institute of Mental Health investigators for the treatment of children with depression (TADS Jr) study.
2. **Draft** protocol addendum B1Y-MC-HCLU(1): A Study of Sexual Maturation in Children Enrolled in the Treatment of Children with Depression (TADS Jr.) Protocol.

Paper copies will be made available upon request. Please let me know if you wish us to supply copies of these documents to any other person or agency.

If you have any questions, please do not hesitate to contact me.

Yours sincerely,

Dr Carly Anderson
Acting on behalf of Dr Diane Mackleston for Eli Lilly and Company fluoxetine MAHs.

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Protocol Addendum B1Y-MC-HCLU(1)
A Study of Sexual Maturation in Children Enrolled in the Treatment of Children with Depression (TADS Jr.) Protocol

Fluoxetine Hydrochloride (LY110140)

Eli Lilly and Company
DRAFT

This addendum is to be performed in addition to all procedures required by the TADS Jr. protocol or any subsequent amendments to that protocol.

Protocol Addendum B1Y-MC-HCLU(1)
A Study of Sexual Maturation in Children Enrolled in the Treatment of Children with Depression (TADS Jr.)
Protocol

Table of Contents

1. Rationale for Addendum

Delayed sexual maturation has been observed in toxicology studies conducted in juvenile rats administered fluoxetine. Lilly believes that the findings of testicular toxicity observed in the juvenile toxicology study with fluoxetine cannot easily be extrapolated to human exposure; however, the Committee for Medicinal Products for Human Use (CHMP) have requested additional safety information regarding sexual maturation in children and adolescents. On 31 May 2006, Lilly made a commitment to the CHMP to further investigate sexual maturation as a secondary endpoint in an independent study of children ages 8 to 12 years diagnosed with major depressive disorder (MDD).

This additional safety measure investigating sexual maturation is sponsored by Lilly and patients will be required to sign a separate consent form to be included in this addendum.

Participation in this addendum is not required for patients enrolled in the TADS Jr. study.

2. Protocol Additions

2.1. Additional Safety Measure

The evaluation of sexual maturation for this Addendum is by Tanner staging performed by a trained medical professional.

Patients' stage of sexual maturation will be assessed by utilizing the Tanner staging measure for determining pubertal development in male and female patients (Tanner and Davies 1985; Tanner 1987). Tanner staging will include a clinical assessment of pubic hair development (both males and females), genital development (males), and breast development (females). The stages of development for each element assessed will be entered on the CRF. For female patients, the trained medical professional also will ask status and date of menarche and will enter the response on the CRF. For male patients, the trained medical professional will measure testicular volume using an orchidometer.

This additional evaluation using Tanner staging will occur at three time points during the TADS Jr. study:

- Visit Gate C (last baseline)
- End of the 12-week double-blind treatment period
- End of the 6-month post-treatment period.

2.2. Study Population

Patients must meet all inclusion and exclusion criteria for the TADS Jr. study in order to be evaluated as part of this addendum. For this addendum specifically, the following inclusion and exclusion criteria must be met in order to participate.

2.2.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria:

[1] Are enrolled in the TADS Jr. study.

[2] Are randomized to either the fluoxetine in combination with CBT or the placebo in combination with CBT treatment groups within the TADS Jr. study.

[3] Have a baseline Tanner stage less than 5.

2.2.2. Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

[4] Have a medical history of a condition known to influence sexual maturation (for example, Klinefelter's syndrome or Turner's syndrome).

[5] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[6] Are Lilly employees.

2.3. Sample Size and Statistical Methods

2.3.1. General Considerations

Statistical analysis of this addendum will be the responsibility of Lilly.

Safety analyses will be conducted on the data from patients randomized to either fluoxetine in combination with CBT or placebo in combination with CBT. Patients receiving no study drug will not be evaluated. This set includes all data from all randomized patients having both a baseline and post-baseline Tanner stage evaluation according to the treatment the patients were assigned, regardless of compliance to therapy. Patients with a baseline Tanner stage of 5 should be discontinued from Addendum HCLU and no further Tanner staging should take place for these patients. If by error, a patient receives the opposite drug throughout the study than the one assigned in the randomization sequence, then the patient will be counted in the treatment group that the patient actually received as long as this is the policy of the TADS Jr. primary researchers.

Investigators with few randomized patients per treatment group may be pooled for statistical analysis purposes. The number of patients and pooling of sites will be consistent with the policy of the TADS Jr. primary researchers.

All tests of treatment effects will be conducted at a two-sided alpha level of 0.05, unless otherwise stated.

2.3.2. Patient Characteristics

Patient age, gender, and baseline Tanner stage will be compared between treatment groups using numerical summaries. For age (and any other continuous baseline variable made available by the TADS Jr. investigators), the mean response by therapy will be compared using a t-test. For gender, the count and percentage of patients will be

compared using Fishers exact test. For baseline Tanner stage, both a summary by count of each stage and comparison of means using a t-test will be made for the treatment groups.

2.3.3. Primary Outcome and Methodology

The primary outcome is considered a safety outcome. The primary analysis variable will be whether a patient has an increase in Tanner stage during the double-blind portion of the study. The proportion of patients treated with fluoxetine in combination with CBT who have an increase in Tanner stage from baseline to endpoint will be compared with the proportion of patients treated with placebo in combination with CBT. The primary statistical test will be a Mantel-Haenszel test of difference in proportions stratified by site.

The analysis of Tanner stage after the open-label, long-term follow-up will be made using the same test. Only patients with both a baseline and a long-term follow-up will be included in the analysis. Secondarily, a comparison will be made of baseline to the last observed post-baseline Tanner stage.

3. References

Tanner JM. 1987. Issues and advances in adolescent growth and development. J Adolesc Health Care 8:470-478.

Tanner JM and Davies PSW. 1985 Clinical longitudinal standards for height and height velocity for North American children. J Pediatr 107:317-329.

Treatment of Children with Depression (TADSJr)

DRAFT PROTOCOL

National Institute of Mental Health

September 27, 2006

Primary Objective:

Our **primary specific aims** are:

1. To compare the short-term effectiveness of CBT alone to CBT + FLX in reducing symptoms of depression and associated functional impairment in patients who are non- or partially responsive to brief CBT. We hypothesize that CBT+FLX will be superior to CBT alone.
2. To compare the short-term efficacy of CBT +FLX to CBT + PBO in reducing symptoms of depression and associated functional impairment in patients who are non- or partially responsive to brief CBT. We hypothesize that CBT+ FLX will be superior to CBT + PBO.
3. To examine the acceptability, tolerability and safety of CBT + FLX to CBT + PBO and to CBT alone.

Secondary Objective(s):

Our **secondary specific aims** are:

1. To examine openly the extent to which brief CBT ameliorates symptoms of depression.
2. To explore predictors of response, including demographics, age of onset, comorbidity, negative automatic cognitions, initial severity, and parental and family psychopathology
3. To examine time to remission from the inception of open treatment, using clinician ratings
4. To examine long-term naturalistic outcomes of CBT, CBT + PBO and CBT + FLX.

Study Background and Rationale:

This proposed study evaluates outcomes of the treatment of depression with cognitive-behavior therapy and fluoxetine, individually and in combination, in children ages 8-12. Following near completion of the Treatment for Adolescents with Depression Study (TADS) the proposal is submitted by the TADS team in concert with the Child and Adolescent Psychiatry Trials Network (CAPTN). The proposal continues and extends the work of a specialized network devoted to understanding the impact of evidence-based treatments on the short and longer term outcomes in children and adolescents with depressive disorders.

Justification: Major depression, which causes clinically significant distress and impairment affecting school, social, and family functioning, is one of the more common and functionally impairing conditions affecting children, with point prevalence estimates ranging from 1 to 3%. Left untreated, depression in children presages persistent, depression, anxiety disorders, conduct disorders and, in some cases, substance abuse extending into late adolescence and adulthood. While suicide is rare in children, depression is an important contributor to suicidality. Hence, effective treatments for depression in children promises to alleviate and perhaps to prevent morbidity and even mortality. In randomized controlled trials, we and others have shown that two monotherapies, cognitive-behavioral therapy (CBT) and the selective serotonin reuptake inhibitor fluoxetine (FLX), are effective treatments for depression in children and adolescents. While 40% of patients will respond early to CBT alone, a substantial proportion of patients treated with CBT alone remain symptomatic and, thus, may benefit from combined treatment. Treatment guidelines universally recommend beginning with CBT in children, adding medication after 4 to 8 weeks if response to CBT alone is inadequate. To test the hypothesis that FLX + CBT is superior to continued CBT, we propose a 12 site, randomized controlled effectiveness trial comparing CBT + FLX to CBT + PBO and to CBT alone in youth age 8 to 12 with depression who are non- or partially responsive to six weeks of CBT.

Although cost and administrative complexity are greater for a multi-site than a single site clinical trial, there are four reasons for using this collaborative mechanism in this instance: (1) Collaboration across disciplines, (thereby increasing credibility) and synergism between the study teams (thereby increasing scientific rigor), provides a model for multidisciplinary clinical and research practice. We also believe that cooperative research efforts among psychologists and psychiatrists will contribute to greater willingness by both professions to utilize the results of our study. (2) Multiple sites are required to recruit sufficient subjects in a timely fashion. (3) The study is powered to find between-group differences on the specified treatment conditions for combined site data. Hence, both the feasibility and the generalizability (external validity) of the study depend on the sampling frame, which encompasses the range of factors associated with the sites (e.g. wide geographical differences, semi-rural and urban, ethnicity, SES etc.). Furthermore, the ability to segment response (e.g. identify moderator variables) is predicated on a sampling frame that encompasses potentially interesting predictive subgroups. (4) Rigorous cross-site quality controls will demonstrate the transportability of treatments among the 12 clinical sites.

Study Design

This is a 12 site, randomized controlled effectiveness trial comparing CBT + FLX to CBT + PBO and to CBT alone in youth age 8 to 12 with depression who are non- or partially responsive to an initial six weeks of CBT.

Stage I is a 6 week open treatment with CBT. In **Stage II**, patients who remain symptomatic will be randomized to 12 weeks of: (1) CBT alone (n = 120), CBT + PBO (n = 120) or CBT + FLX (n = 120). (Responders at the end of Stage I will have CBT faded and will be followed openly.) In **Phase III**, patients who will have received clinically appropriate end-of-treatment recommendations and will continue to be treated and then assessed 6 months later

- Coordinating Center: John March;
- Baystate Medical Center/Tufts: Bruce Waslick;
- Case Western Reserve University: Norah Feeny;
- Duke University: John Curry;
- Columbia University: Anne Marie Albano;
- Johns Hopkins University: Golda Ginsburg;
- Judge Baker/Harvard: John Weisz;
- University of Nebraska: Christopher Kratochvil;
- Northwestern University: Mark Reinecke;
- University of Cincinnati: Sanjeev Pathak;
- UT Galveston: Karen Wagner;
- UT Southwestern: Graham Emslie;
- UCLA: Joan Asarnow.

Randomization Design

Nonresponders or partial responders to CBT after 6 weeks randomized 1:1:1 to CBT alone, CBT + PBO, or CBT + FLX

Study Population

Children 8-12 years of age with major depressive disorder.

Major Inclusion Criteria:

Age 8-12 inclusive
DSM-IV diagnosis if MDD or MDD NOS
CDRS-R total score $\geq$ 40
Full scale IQ > 80
Outpatient
English-speaking child

Major Exclusion Criteria:

Other primary psychiatric disorder
Bipolar I in first or second-degree relative
Pervasive developmental disorder
Thought disorder
Concurrent treatment with psychotropic medication other than stable dose of psychostimulant, or psychotherapy outside of study

Methodology:

Measures By Domain, Variable Type And Rater

MEASURE	*Domain*	*Who*	*Gates*	*Baseline*	*During Tx*	*Post-Tx*
			A, B	*Gate C*		
Phone screen	In/Exclusion	SC	X			
Demographics, IQ, history	Caseness	SC, IE	X			
Treatment history	Caseness	T	X			
KSADS	Caseness/Comorbidity	IE	X		X	X
CDRS-R	MDD	IE	X	X	X	X
QUIDS	MDD	CCP	X	X	X	X
Clinical Global (CGI-I and CGI-S)	MDD	T		X	X	X
Height & Weight	Growth	SC		X	X	X
Physical Examination	Health Status	T		X		X
CGA	Functional impairment	C, P		X	X	X
Expectancy Ratings—Drug	"Non-specific" effects	C, P, T		X		
Expectancy Ratings—PS	"Non-specific" effects	C, P, T		X		
Consumer satisfaction	Consumer satisfaction	C, P		X	X	X
IE Blindness	IE Blind	IE				
TX Compliance						
Therapeutic Alliance						
Family History Screen (DX)	FH Mental Illness	T		X	X	X
CATQ	Negative Automatic Thoughts					
Life Event						
Conners Parent Rating Scale	Disruptive behaviors	P		X	X	X
BSI	Parent psychopathology	A		X	X	X
Family Assessment Measure	Family functioning	P		X	X	X
IQ (vocab, block design)	IQ		X			
PAERS	Adverse Events	T		X	X	X

SC = study coordinator; T = clinician rated, Child = child self-report, Adult = adult self-report, IE = independent evaluator rated, P-Parent rated

Primary Study Endpoint:

CDRS-R change (magnitude)
CDRS-R $\leq$ 28 (remission)

Secondary Study Endpoint(s):

Tolerability
Functional impairment
Satisfaction with treatment.

Sample Size and Justification:

The protocol assumes 500 subjects started in Stage I, assumes approximately 30% full response rate at the end of Stage I, resulting in the "n" required to reach 360 randomized subjects (50 per site, 10 per year, adjusted over 5 years). With 120 subjects per treatment group, the study will have 80% power to identify a 20% difference in response rate at the end of Stage II, assuming 10% attrition and a 2 tailed alpha of .05.

Coordinating Center

TADSJr will be coordinated by an experienced team at the Duke Clinical Research Institute (DCRI). Overall administrative responsibility will rest with the Coordinating Center (CC) PI (John March) the CC Principal Statistician (Susan Silva), and Project Leader, Mark Shapiro. DCRI will have responsibility for training as well as data management. Collaborating scientists from the CC and each of the 12 clinical sites will form the Steering Committee (SC) for the project. The SC will provide scientific and practical oversight for TADSJr.

Data Analysis Plan:

The primary effectiveness and safety analyses will be conducted using an "intention-to-treat" (ITT) principle in which the analysis included all randomized patients in the treatment arms to which they were randomly assigned, regardless of their protocol adherence, actual treatment received, and/or subsequent withdrawal from treatment, assessments, or deviations from protocol. To minimize confounding by treatments administered under the adjunctive services and attrition prevention provisions of the protocol, we will conduct supplementary analyses using an "observed cases" (OC) principle in which the analysis included only those data elements for which the patient was still in his or her assigned treatment arm at the time of the assessment. As in the TADS, the primary analyses will employ random coefficients regression models for scalar or binary outcomes. The primary endpoints will be predicted scores for response at the end of Stages II and III. Specifically, the impact of treatment on outcome will be modeled as a function of fixed effects for treatment, time, and clinical site (and their two-way and three-way interaction terms) as well as the random effects for patient and patient by time interactions. Time will be defined as the natural log of days since randomization. Where appropriate, the final model will include both linear and quadratic time effects (and their significant interactions), depending on whether the quadratic term is statistically significant. Site will be retained but its interactions will be omitted from the final model if statistically non-significant. Generalized estimating equations (GEE) for binary outcomes will be used to compare the probability of treatment response over time in the three treatment arms. The GEE model will include treatment, time, treatment by time, and site. For the binary outcomes, if the time effect is curvilinear, a quadratic term will be included in the model. As necessary, sites will be collapsed to improve the stability of the model. Both RR and GEE models are tolerant to missing data in the dependent variable. No imputation methods will be used other than predicted scores based on the within-subject slope terms.

Ethical Considerations:

- Inclusion of children.
- Inclusion of patients with depression.
- Use of antidepressant.
- Use of placebo.

Number of Sites: 12
Expected Number of Subjects to be Screened: 1,100
Expected Number of Subjects to be Enrolled: 500 enrolled into open treatment with CBT, 360 randomized
Expected Number of Subjects to Complete Study: 300
Duration of treatment: 9 months of pharmacotherapy
Dosing Schedule and Frequency: FLX 10mg per day for one week, then increase to 20mg per day, as tolerated, for the duration of the study.
Study Visit Schedule and Visit Window • Gate A (telephone screen) • Gate B (assessment/caseness): 1-28 days after Gate A • Gate C (randomization): 7 days after Gate B (up to 28 days) • Stage I: CBT visits weekly x 6 weeks • Stage II: CBT visits weekly x 12 weeks; medication management visits weekly x 4 weeks, then q 2 weeks x 4 weeks, then at 12 weeks • Stage III: Booster CBT and medication management every 6 weeks x 24 weeks

Addendum #1: Site Selection Procedure

Purpose

The site selection process is a multi-phased process. In preference to an expensive on-site evaluation, TADS uses a written and telephone process to evaluate and select sites. The following document outlines the process used for this trial, which fulfills the DCRI Standard Operating Procedures 20006 (Investigator Recruitment) and 20002 (Pre-Study Evaluation).

TADSJr Site Selection Team

TADSJr Site Selection Team (SST) is comprised of the Coordinating Center PI (John March), Statistical PI (Susan Silva), DCRI Project Leader (Mark Shapiro) and the Chairs of the CBT (John Weisz), PT (Graham Emslie), Assessment (Mark Reinecke) and Pharmacy (John Walkup) Committees.

Procedure

I. Initial interest and screening:

A. Extant sites from TADS: Case Western Reserve University: Norah Feeny; Children's Hospital of Philadelphia: Elizabeth Weller; Columbia University: Anne Marie Albano; Johns Hopkins University: John Walkup; University of Nebraska: Christopher Kratochvil; Northwestern University: Mark Reinecke; University of Cincinnati: Sanjeev Pathak; University of Texas Southwestern: Graham Emslie

B. Potential sites many of which had expressed interest already were contacted by the CC to ascertain their interest in participating and their level of experience with adolescent depression: Duke University: John Curry, UT Galveston: Karen Wagner, Baystate Medical Center/Tufts: Bruce Waslick; UNY Stonybrook: Gaye Carlson; Judge Baker/Harvard: John Weisz; WPIC: David Brent; Kaiser: Greg Clarke; UCLA: Joan Asarnow: U Wisconsin: Marcia Slattery

II. Formal Site Evaluation (WebBased Questionnaire)

A. CC Verification of site's qualification (See Questionnaire)

1. Review experience and training of site PI and other personnel
2. Discuss enrollment requirements and timelines to assess feasibility
3. Discuss potential conflicting studies
4. Assure PI is not disqualified by FDA
5. Assess site's client population (gender, race, setting)
6. Financial, insurance and contractual issues
7. Assure site can comply with IRB requirements
8. Guarantee adequate and secure drug storage
9. Assure site has adequate and secure patient data storage
10. Insure electronic data capture capability
11. Insure MedAvante videoconferencing capability

B. Generate composite score for sites on 5 categories:

1. Research experience at site
2. Feasibility of meeting trial requirements
3. Practice diversity

4. Staff qualifications
5. Competing trials

C. Other factors included in rating sites:
1. Geographic location
2. Coordinating Center's knowledge of sites

D. Final selection:
1. Information reviewed by TADSJr Site Selection Team
2. Consensus reached for 12 active sites

III. Evaluation Report

A. Written report on each site to include:
1. Date of evaluation
2. Name and address of PI at site
3. Name of individual writing
4. Summary of findings

B. Send follow-up letters to sites

Addendum #2: Tentative Timeline for Study Completion

- **If funded after first NIMH review**
  - February 2007: submit to NIMH
  - June 2007: review by NIMH study section
  - October 2007: review by Council
  - January 2008: funds available and start study
  - February 2008: study startup & training
  - March 2008 to April 2012: study enrollment
  - July 2012: last patient visit, acute phase
  - January 2013: last patient visit, extension phase
  - March 2013: data cleaning complete
- **If funded after second NIMH review**
  - February 2007: submit to NIMH
  - June 2007: review by NIMH study section
  - February 2008: submit revision
  - June 2008: review by NIMH study section
  - October 2008: review by Council
  - January 2009: funds available and start study
  - February 2009: study startup & training
  - March 2009 to April 2013: study enrollment
  - July 2013: last patient visit, acute phase
  - January 2014: last patient visit, extension phase
  - March 2014: data cleaning complete
  -
- **If funded after third NIMH review**
  - February 2007: submit to NIMH
  - June 2007: review by NIMH study section
  - February 2008: submit revision
  - June 2008: review by NIMH study section
  - October 2008: submit revision
  - February 2009: review by NIMH study section
  - June 2009: review by Council
  - September 2009: funds available and start study
  - October 2009: study startup & training
  - November 2009 to December 2013: study enrollment
  - March 2014: last patient visit, acute phase
  - September 2014: last patient visit, extension phase
  - November 2014: data cleaning complete