1 TITLE PAGE

RANDOMIZED, MULTICENTER, DOUBLE-BLIND, COMPARISON STUDY OF THE EFFICACY AND SAFETY OF DEROXAT® (PAROXETINE) AND ANAFRANIL® (CLOMIPRAMINE) IN THE TREATMENT OF UNIPOLAR MAJOR DEPRESSION IN ADOLESCENTS 12 TO 20 YEARS OF AGE.

STUDY DRUG:	Paroxetine hydrochloride
INDICATION:	Unipolar major depression in adolescents 12 to 20 years of age
METHODOLOGY:	Phase III, randomized, multicenter, double-blind, controlled study versus clomipramine in two parallel groups stratified by age bracket, for 56 days to a maximum of 168 days, with direct individual benefit.
SPONSOR:	SmithKline Beecham 6, Esplanade Charles-de-Gaulle 92731 Nanterre cedex
PROTOCOL:	CPMS # 29060/511
FIRST PATIENT ENROLLED ON:	*March 17, 1997*
LAST PATIENT ENROLLED ON:	*December 21, 1998*
STUDY PHASE:	*Phase III*
SPONSOR'S STUDY COORDINATOR:	XXXXXXXXXX

There was no previous clinical report on this study. This study was conducted in accordance with the Good Clinical Practices in effect in France on the date it was initiated.

DATE OF THIS REPORT: May 22, 2000

Phase III, randomized, multicenter, double-blind, controlled study versus clomipramine in two parallel groups stratified by age bracket, for 56 days to a maximum of 168 days, with direct individual benefit.

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Doctor XXXXXX

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XXXXXX SIGNATURE:

DEPARTMENT:

XXXXXX DATE:

2 SYNOPSIS

Name of company/sponsor: SmithKline Beecham	Individual study table referring to part of the dossier:	(For National Authority use only)
Name of drug product: Deroxat®	Volume:	
Name of active ingredient: Paroxetine	Page: 1	

Study title:	Randomized, multicenter, double-blind, comparison study of the efficacy and safety of Deroxat® (paroxetine) and Anafranil® (clomipramine) in the treatment of unipolar major depression in [adolescent] patients 12 to 20 years of age.
Investigators:	- XXXXXXXXXXXX - 38 investigators - psychiatrists and child psychiatrists, hospital practitioners, private practitioners or PMC practitioners.
Study centers:	39 centers, including 23 hospitals, throughout France
Publications (references):	-
Studied period (years): 1997 - 1998 Date of first enrollment: March 17, 1997 Date of last enrollment: December 21, 1998 Date of last visit: April 28, 1999	Clinical development phase: III
Study objectives:	Comparison of the efficacy and safety of Deroxat® (paroxetine) and Anafranil® (clomipramine) in the treatment of unipolar major depression in adolescents 12 to 20 years of age.
Methodology:	Phase III, randomized, multicenter, double-blind, controlled, double placebo study versus clomipramine in two parallel groups stratified by age bracket, for 56 days (to a maximum of 168 days), with direct individual benefit.
Number of patients (planned and analyzed):	150 patients planned, 121 analyzed.
Diagnosis and main criteria for inclusion:	• Patients from 12 to 20 years of age; • Unipolar major depression, defined according to the DSM-IV criteria; • MADRS score ∅24 at the selection visit. This score had to still be $\geq$ 24 at the enrollment visit and was not to have decreased by more than 20% since selection.
Test product: dose and mode of administration, batch number:	• Deroxat® 20-mg tablet, - 1st period of 21 days = 20 mg of Deroxat® (one tablet in the morning), - 2nd period of 35 days = 20 or 40 mg of Deroxat® (one or two tablets in the morning). - After D56 until D168 maximum: the treatment was either continued at the same dosage, modified, or discontinued, depending on the response. • Oral route • Deroxat® = lots 427 and 620, Placebo = lactose 25612 • Expiration date: lot 427: 08/05/1998; lot 620: 01/12/2000

Name of company/sponsor: SmithKline Beecham	Individual study table referring to part of the dossier:	(For National Authority use only)
Name of drug product: Deroxat®	Volume:	
Name of active ingredient: Paroxetine	Page: 2	

Duration of treatment: *(for both treatments)*	• Efficacy evaluation = up to 56 days. It involved all of the patients, including those whose treatment was extended up to 168 days. • Safety evaluation = up to 168 days.
Reference therapy: dose and mode of administration, batch number:	Anafranil® 75-mg tablet 1st period of 21 days = 75 mg of Anafranil® (1 tablet in the evening) 2nd period of 35 days = 75 or 150 mg of Anafranil® (1 or 2 tablets in the evening) After D56 until D168 maximum, the treatment was either continued at the same dosage, modified, or discontinued, depending on the response Oral route Anafranil® = lot: T6023; placebo = lactose 256121 Expiration dates: lot T6023: March 2001; lot T7061: 10/01/2002
Criteria for evaluation EFFICACY	- PRIMARY CRITERION: • number of complete responders: improvement in the MADRS score by at least 50% compared with the baseline score at the enrollment visit. • Clinical Global Impression (CGI) at D56 - SECONDARY CRITERIA: • MADRS scales from the enrollment visit to D56 and upon discontinuation of treatment. • HSCL-58 self-report at D21, D56, and until discontinuation of treatment. • GAF questionnaire from enrollment to D56, at each visit, if applicable at D168. • number of treatment failures in both groups. • number of non-responders in both groups.
SAFETY	Evaluation and comparison of Deroxat® and Anafranil®, by recording Intercurrent Events.
Statistical methods	- N was calculated for [an] expected difference of 25% between the 2 treatments, with stratification according to age bracket, or 120 evaluable patients - Two-tailed tests with ζ = 5% and power = 80% - Evaluation of efficacy over 56 days and of safety over a maximum of 168 days. - Tests used = qualitative variables: chi-squared test quantitative variables: Student's t test or Wilcoxon rank-sum test, logistic regression and ANOVA for repeated measurements
EFFICACY RESULTS	- The number of complete responders on D56 was greater in the Deroxat® group than in the Anafranil® group (p=0.06 for the ITT population, p=0.01 for the per protocol population). - The improvement in the MADRS score was greater in the Deroxat® group, which was demonstrated by logistic analysis (p=0.026). Similarly, the analysis of variance revealed a greater decrease in the MADRS over time in the Deroxat® group (p=0.003). - The patients' condition improved (psychological, social, and occupational functioning) in both groups, but with no significant difference between the two (GAF). - The percentages of global improvement of the disease were comparable in the two groups (CGI).

SAFETY RESULTS	- Emergent intercurrent events: 97 patients presented with 314 events; their incidence was in keeping with the known characteristics of the two study treatments. - Serious intercurrent events: 22 patients presented with 32 serious intercurrent events. No statistically significant difference was observed between the two treatment groups (p=0.47). - Among all of these events, 67 were deemed severe by the investigator, and no significant difference between the two treatment groups was observed. Nor was there any difference between the two treatment groups with respect to the number of discontinuations of treatment related to an intercurrent event. The intercurrent events related to Deroxat® were fewer than those associated with Anafranil® (p=0.03) in bracket 2, except for the events that were described as severe by the investigator, for which the distribution between the two groups was equivalent.
CONCLUSION	- This study therefore demonstrated that the efficacy of Deroxat® is at least equivalent to that of Anafranil® for treating unipolar major depression in young subjects (12 to 20 years of age), and that the safety profile of Deroxat® is in keeping with the product's characteristics.
Date of the report:	MARCH 24, 2000

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4 LIST OF ABBREVIATIONS

CCPPRB	Comité de Consultation des Personnes se prêtant à la Recherche Biomédicale [sic] [*Advisory Committee for the Protection of Human Subjects in Biomedical Research- Equivalent of IEC or IRB*]
CDI	Children's Depression Inventory
CGI	Clinical Global Impression
CRA	Clinical Research Assistant
GAF	Global Assessment of Functioning
HDRS	Hamilton Depression Rating Scale
HSCL-58	58-item Hopkins Symptoms Checklist for anxiety
IE	Intercurrent Event
ITT	Intent To Treat
LOCF	Last Observation Carried Forward
MADRS	Montgomery and Asberg Depression Rating Scale
MAOI	Monoamine Oxidase Inhibitor
PMC	Psychiatric Medical Center
PP	Per Protocol
SAE	Serious Adverse Event
SRI	Serotonin Reuptake Inhibitor
WHO	World Health Organization

5 ETHICS

5.1. Comité Consultatif de Protection des Personnes se prêtant à des Recherches Biomédicales [CCPPRB]

The DEROXADO study protocol (Appendix 16.1.1) and the final version of the patient information sheet and consent forms were approved on 09/06/1996 by XXXXXX XXXXXX.

A copy of the approval is provided in the appendices (Appendix 16.1.2).

The CCPPRB was informed of four amendments to the protocol (see copy in the appendices).

These amendments were:

- Amendment no. 1: - DSM-IV assessment scale,
  - patient recruitment method (PMCs).

- Amendment no. 2: - selection criterion (outpatient or inpatient).

The first two amendments were submitted while the protocol was in the process of being reviewed by the CCPPRB.

- Amendment no. 3: - self-rating scale: CDI,
  - selection criterion: Tanner stage II instead of stage IV,
  - neuropsychological and therapeutic exclusion criterion, new definition of authorized and prohibited psychotherapies,
  - authorized and prohibited co-prescriptions. Details regarding the co-prescriptions ultimately authorized appear in section 9.4.7.

- Amendment no. 4: - definition of the ITT population,
  - analysis of the “anxiety” and “depression” dimensions of the secondary HSCL-58 criterion.

Amendments 3 and 4 were submitted during the course of the study.

5.2 The Ethical Nature of the Study

This study was conducted in conformity with the principles established by:

- the Declaration of Helsinki amended at the assemblies of the World Medical Association in Tokyo (1975) and in Venice (1983),

- Huriet Law No. 88-1138 of December 20, 1988, supplemented by the law of January 23, 1990, and implemented by Decree No. 90-872 of September 27, 1990.

5.3 Patient Information and Informed Consent

The patients and both parents or their legal representatives were informed by a notice understandable to each of them (Appendix 16.1.13), and their consent was obtained and signed (Appendix 16.1.13) in the investigator's presence during the selection visit.

The investigator also informed them verbally of the principles and the goal of the study, its duration, the necessary exams, the possible risks and benefits, the treatments administered, and the use of the data obtained.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The coordinator was XXXXXX

Thirty-eight other investigators (twenty-three hospital practitioners and fifteen private practitioners) participated in this study.

Of these thirty-nine centers, twenty-four recruited at least one patient. The other centers (n=15) did not enroll any patients.

The list of all of the investigators is presented in the appendices (16.1.4).

The Laboratoires SmithKline Beecham physician in charge of the project was XXXXXX
XXXXXXThe trial was initiated by XXXXXX

The trial was monitored by CRAs from XXXXXX

The statistical analysis was performed by statisticians from XXXXXX

7 INTRODUCTION

The prevalence of depressive disorders in the adolescent population varies from one study to another, but it is always described as significant. There is a large degree of polymorphism with respect to the complaints that lead an adolescent and/or the parents to consult a physician, requiring the clinician to systematically check for the usual clinical signs of depression in order to make or not make the diagnosis. Several factors can explain the frequent failure to recognize depression in adolescents: not seeking care or even refusing to seek care, frequent comorbidity, frequent mingled combinations of sadness, pain, tension, and irritability, defense or denial masking the mood disorder, and difficulty in the initial assessment in distinguishing between a depressive state and typical adolescent behavior.

The role of antidepressants in the treatment of mild or moderate disorders remains a subject of controversy. But the use of antidepressants in this age bracket is recommended in the event of a failure to respond rapidly to psychotherapy, in the case of severe or prolonged depression, in the event of suicidal tendencies, or in the case of problems with social, family or academic integration processes.

Alternative treatments to tricyclic antidepressants in the depressed adolescent are currently being studied. These include MAOIs (Monoamine Oxidase Inhibitors) and SRIs (Serotonin Reuptake Inhibitors). Due to their specific inhibiting action, SRIs produce serotoninergic modulation. AMBROSINI (5) reported his preference for SRIs over tricyclics for adolescents with a risk of suicide or loss of control over their impulses[i], the reason for this preference being the lack of interaction with alcohol, the better tolerance, and the lower risk in the event of an SRI overdose. The fact that SRIs induce fewer side effects than tricyclics should encourage good treatment compliance in these young patients. In a double-blind study versus placebo, EMSLIE (10) reported that fluoxetine was demonstrated to be effective for treating depression in children and adolescents.

Paroxetine is one of the most potent and most selective SRIs, and it has demonstrated its efficacy in the treatment of depressive disorders in adults in several controlled studies[ii] [iii] [iv] [v]. Paroxetine also has few side effects and is well tolerated - characteristics common to all the SRIs. In the study by BOYER and BLUMHARDT, no adverse effect was reported in the youngest patients. However, the small number of patients under 18 years of age in these studies, as well as the diverse methodologies employed, make it difficult to draw any definitive conclusion regarding the efficacy of paroxetine in this population.

It is because of this dual need, for effective and well-tolerated treatments for depression in adolescents, and for more information in this age bracket, that Laboratoires SmithKline Beecham implemented this phase III protocol.

8 STUDY OBJECTIVES

8.1. Primary Objective

The primary objective of this study was to compare the efficacy and tolerance of Deroxat® 20 mg (paroxetine) and Anafranil® 75 mg (clomipramine) after a 56-day treatment administered orally to patients 12 to 20 years of age with unipolar major depression.

The efficacy of Deroxat® was compared to that of Anafranil® on D56 based on the following criteria:

• Number of complete responders, defined as the number of patients who had an improvement in their Montgomery and Asberg scale (MADRS) score of at least 50% compared with their baseline score at the enrollment visit.

• Clinical Global Impression score (CGI) on D56.

8.2. Secondary Objective

The secondary objectives of this study were:

• With respect to efficacy:

- the change in comparison to the enrollment visit of the MADRS scores at D7, D21, D28, D42, D56, and during the follow-up phase, after D56, on the final discontinuation of treatment or termination of the study; comparison in the two treatment groups.

- the comparison in the two treatment groups of the Clinical Global Impression score at D21, at D56, and during the follow-up period, after D56, until the final discontinuation of treatment or termination of the study.

- the comparison in the two treatment groups of the change in the HSCL 58 self-report at D21, D56, and during the follow-up phase, on the final discontinuation of treatment or termination of the study.

- the change in comparison to the enrollment visit of the Global Assessment of Functioning (GAF) score at D7, D21, D28, D42, D56, and on the final discontinuation of treatment or termination of the study; comparison in the two treatment groups.

- the number of treatment failures (early, late) and comparison in the two treatment groups.
Failures were defined as the need to discontinue the study treatment, change the antidepressant or add another psychotropic agent due to a lack of clinical improvement, poor tolerance of the study treatment, or a suicide attempt. Among the failures, a distinction was made between early failures (occurring between D21 and D56) and late failures (occurring during the follow-up period, after D56, up to the final discontinuation of treatment).

- the number of non-responders and comparison in the two treatment groups.

• With respect to safety:

- the evaluation and comparison of the clinical tolerance of Deroxat® and Anafranil® over the entire duration of the study.

9 INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan: Description

This phase III, randomized, multicenter study was intended to compare, under double-blind conditions, the efficacy and tolerance of Deroxat® and Anafranil® in 150 adolescents 12 to 20 years of age who were suffering from depression, defined according to the DSM-IV criteria, and whose MADRS scores were greater than or equal to 24.

A selection visit was made at D-7 to ensure that the selection criteria had been met and to inform the patients and obtain the written consent of both parents and the adolescent. The consent of both legal guardians was not obtained for patients who were of legal age (>18 years old). In the event that only one parent exercised parental authority, it was that parent's signature that was required. On the day of enrollment, D1, the inclusion/exclusion criteria were verified and an assessment of the baseline condition was performed; the treatments were assigned, with stratification by age bracket (bracket 1 = 12 to 15 years and 11 months; bracket 2 = 16 to 20 years and 11 months).

The treatment was then given out, after randomization according to a double-placebo procedure:

for the patients in the Deroxat® group:	- 1 20-mg Deroxat® capsule in the morning, - 1 Anafranil® placebo capsule in the evening.
for the patients in the Anafranil® group:	- 1 Deroxat® placebo capsule in the morning, - 1 75-mg Anafranil® capsule in the evening.

The patients were then evaluated at D7, D21, D28, D42, and D56.

On D21, if tolerance was satisfactory, the dose of Deroxat® or Anafranil® was doubled (i.e., 40 mg of paroxetine or 150 mg of clomipramine) if the investigator deemed this necessary in terms of efficacy.

Beyond D56, the end point of the efficacy evaluation period, treatment was either continued at the same dosage, changed, or discontinued, depending on the response. During this second period, which totaled a maximum of 112 days, an evaluation of the tolerance was performed every month until the final discontinuation of treatment.

A chart representing the study design is as follows:

EXECUTION OF THE DEROXADO STUDY FROM D-7 to D168

VISIT DATE	SELECTION D-7	INCLUSION D1	D7 (∂ 2 days)	D21 (∂ 2 days)	D28 (∂ 2 days)	D42 (∂ 2 days)	D56 (∂ 2 days)	D84 (∂ 7 days)	D112 (∂ 7 days)	D130 (∂ 7 days)	D168 (∂ 7 days)	END OF STUDY
WRITTEN CONSENT	X											
MEDICAL HISTORY and CLINICAL EXAMINATION	X	X	X	X	X	X	X	X	X	X	X	
RANDOMIZATION		X										
DIAGNOSIS ACCORDING TO DSM-IV	X											
HDRS		X										
MADRS	X	X	X	X	X	X	X					X
CDI	X	X	X	X	X	X	X					X
GAF		X	X	X	X	X	X					X
CGI				X			X	X	X	X	X	(X)
PATIENT SELF-REPORT (HSCL-58)		X		X			X					X
TOLERANCE												

9.2. Discussion of the Study Design, Including the Choice of Control Groups

In this trial, the population studied consisted of 2 comparison groups, and randomization was performed for each bracket at the enrollment visit.

From D0 to D21, each group took:

- either Deroxat® at a dose of 1 20-mg tablet in the morning and one Anafranil® placebo tablet in the evening,

- or Anafranil® at a dose of 1 75-mg tablet in the evening and one Deroxat® placebo tablet in the morning.

From D21 to D56 maximum:

the dose of Deroxat® or Anafranil® was possibly doubled in each treatment group, if the investigator deemed the tolerance acceptable and the efficacy minimal to nil.

Treatment could be extended to D168, at the investigator's discretion.

This plan was intended to permit the best evaluation of the efficacy (namely, the time until response) and safety of paroxetine compared with Anafranil.

Within each treatment group, stratification by age bracket enabled more information to be gathered regarding the treatment of patients under 18 years of age, given that the clinical studies available to date involved only a few of these young patients, whereas the clinical presence of depression in this age bracket is now recognized.

9.3. Selection of the Study Population

In order to be selected, the patients had to meet the following criteria:

9.3.1. Selection criteria

The patients were 12 to 20 years of age and presented with unipolar major depression defined according to the DSM-IV criteria; their MADRS score had to be greater than or equal to 24. They had to meet the following conditions:

- boy/girl, pubescent (at least Tanner stage II), between age 12 and age 20 years and 11 months inclusive;
- an outpatient or an inpatient at the time of the study treatment;
- weight greater than or equal to 35 kg;
- their motivation to comply with the study treatment was deemed satisfactory by the investigator at the end of the selection period;
- if female and of childbearing age, a negative pregnancy test (urinary and blood) performed the week prior to inclusion.

The patient's written and signed informed consent had to have been obtained, as well as that of the patient's parents or legal representatives (unless the patient was of legal age), after being informed of the study procedures.

9.3.2. Exclusion criteria

Any patient having any one of the following characteristics could not be enrolled in the study:

Neuropsychological:

- ∉ Associated comorbid conduct disorder (including anorexia nervosa and bulimic disorders),
- ∉ Autism,
- ∉ Schizophrenia,
- ∉ Epilepsy,
- ∉ Intense suicidal ideation,
- ∉ History of a suicide attempt using antidepressants having a long half-life during the month prior to inclusion,
- ∉ Obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder,
- ∉ Delusional depression.

General:

- ∉ Any severe disorder (cardiovascular, renal, hepatic, gastrointestinal, metabolic, neurological, auto-immune),
- ∉ Suspected or known glaucoma or urethral-prostate disorder,
- ∉ Known hypersensitivity to the study treatments, [participation in] a clinical trial in the past thirty days,
- ∉ Young woman of childbearing age having sexual relations without effective contraception.

Enrollment in another protocol (clinical investigation in the past 30 days or the equivalent of the duration of 5 half-lives following the last dose of the drug being investigated).

Therapeutic:

- ∉ Formal individual or family psychotherapy (psychoanalysis, cognitive-behavioral therapy) planned during the study,
- ∉ Electroconvulsive therapy prior to or during the study,
- ∉ Ongoing or future treatment with lithium planned during the study,
- ∉ Ongoing or future treatment with anticonvulsants planned during the study,
- ∉ Treatment with MAOIs in the month prior to inclusion or planned during the study,
- ∉ Treatment with atypical antidepressants (oxitriptan (Lévotonine®), viloxazine (Vivalan®), oxaflozone (Conflictan®), mianserin (Athymil®)) for at least three days in the month prior to inclusion or planned during the study,
- ∉ Treatment with a serotonin reuptake inhibitor (including paroxetine) for at least three days in the month prior to inclusion or planned during the study,
- ∉ Treatment with tricyclics (including clomipramine) for at least three days in the month prior to inclusion or planned during the study,

- ∉ Treatment with amphetamine psychostimulants for at least three days in the month prior to inclusion or planned during the study,
- ∉ Treatment with anxiolytics for at least three days in the week prior to inclusion or planned during the study,
- ∉ Treatment with a neuroleptic for at least three days in the week prior to inclusion or planned during the study.

9.3.3. Inclusion criteria

At the end of the selection period, the patients still had to meet all of the selection criteria and none of the exclusion criteria.

In addition, the MADRS score still had to be greater than or equal to 24 and could not have decreased by more than 20% in relation to the selection visit.

9.3.4. Withdrawals from the study and early terminations

The study complied with the protocol if the patients were treated until D56 and if the efficacy and safety evaluation criteria were available for this period.

In the case of early termination, the following evaluations were performed, if possible:

- MADRS, CDI, CGI, GAF, HSCL-58 scales,
- safety.

Early terminations were documented [as follows]:

- adverse event (serious or non-serious), treatment failure, poor compliance, lost to follow-up, protocol violation, withdrawal of the patient's or the parents' consent, decision of the investigator or the sponsor.

9.4. Treatments

9.4.1. Treatments administered

The study treatments necessary for the protocol were prepared by the sponsor. They were packaged in boxes containing the treatment units required for the periods between each visit scheduled in the protocol.

The treatment units were packaged in blister packs and the placebos were included in the treatment boxes.

A detachable label was created that referenced the study and the randomization number.

The products were stored in a suitable locked location, in the investigator's offices or in the hospital's central pharmacy.

The treatment regimen was the following:

		Evaluation **D1 - D21**		Efficacy and Safety **D21 - D56**		Safety Evaluation (optional) **D56 - D168**	
	Treatment	Morning	Evening	Morning	Evening	Morning	Evening
Deroxat® Group	Paroxetine	1 capsule		1 or 2 capsules		1 or 2 capsules	
	Placebo		1 capsule		1 or 2 capsules		1 or 2 capsules
Anafranil® Group	Placebo	1 capsule		1 or 2 capsules		1 or 2 capsules	
	Clomipramine		1 capsule		1 or 2 capsules		1 or 2 capsules

9.4.2. Identity of Investigational Product(s)

Deroxat® (paroxetine): the Deroxat® was supplied in the form of a size-O sealed capsule containing 1 oblong scored film-coated 20-mg tablet of paroxetine hydrochloride and lactose.

The paroxetine placebo was identical in appearance to the active paroxetine.

Up until D21, the dosage was 1 20-mg tablet in the morning with breakfast; then this dosage could possibly be doubled, i.e., 2 times 20 mg of paroxetine or 2 times 1 placebo capsule taken in a single dose.

Anafranil® (clomipramine): the Anafranil® was supplied in the form of a size-O sealed capsule containing 1 oblong scored film-coated 75-mg tablet of clomipramine hydrochloride and lactose.

The clomipramine placebo was identical in appearance to the active clomipramine.

Up until D21, the dosage was 1 75-mg tablet in the evening at bedtime; then this dosage could possibly be doubled, i.e., 2 times 75 mg of clomipramine or 2 times 1 placebo capsule taken in a single dose.

9.4.3. Method of Assigning Patients to Treatment Groups

The randomization was stratified by age bracket:

- patients from 12 to 15 years and 11 months were randomized using numbers 1 to 176,
- patients from 16 to 20 years and 11 months were randomized using numbers 501 to 676.

In each age bracket, the treatment units were assigned to the patients in ascending numerical order.

Thus the randomization number assigned to the patient was directly dependent upon [both] his/her inclusion date and his/her age bracket at the center.

9.4.4. Selection of doses

The dosage, taken in one dose per day, was 20 mg for Deroxat® or 75 mg for Anafranil® from D1 to D21; it could be doubled to 40 mg for Deroxat® or 150 mg for Anafranil® as of D21 until the end of the trial.

A double placebo was provided:

to the patients in the Deroxat® group, one Anafranil® placebo was administered in the evening;
to the patients in the Anafranil® group, one Deroxat® placebo was administered in the morning.

9.4.5. Selecting and Timing of Dose For Each Patient

Up until the 21st day of treatment, the dosage was 1 tablet per day (Deroxat® or Anafranil®).

As of the 21st day, the therapeutic efficacy and safety were evaluated. The decision to double the dose was made based on the following decision algorithm:

- 1st case: adverse effects were absent or moderate and therapeutic efficacy was minimal or nil. The treatment dose was then doubled.

- 2nd case: adverse effects were absent or moderate and therapeutic efficacy was moderate or marked. The patient continued at the same treatment dose.

- 3rd case: adverse effects were significant or very significant and therapeutic efficacy was moderate or marked. The patient terminated the study and was considered a treatment failure.

- 4th case: adverse effects were significant or very significant and therapeutic efficacy was minimal or nil. The patient terminated the study and was considered a treatment failure.

9.4.6. Blinding

There were two types of placebo tablets: Deroxat® placebos and Anafranil® placebos, containing lactose and supplied in the form of a size-O sealed capsule.

Each box of treatment included blister packs of 10 capsules divided into 5 “morning” capsules containing paroxetine, either active or placebo, and 5 “evening” capsules containing clomipramine, either active or placebo.

The boxes were labeled for the following periods:

- D0 - D7 (2 blister packs of 10 capsules)
- D7 - D21 (4 blister packs of 10 capsules)
- D21 - D28 (2 blister packs of 10 capsules)
- D28 - D42 (4 blister packs of 10 capsules)
- D42 - D56 (4 blister packs of 10 capsules)

To continue treatment after D56, the investigator was provided, upon his/her request, with the necessary quantity of active product and placebo, labeled, numbered, and packaged in the same manner as those for the first phase of the study, so as to continue treatment without breaking the blind.

This quantity was renewed every month until the end of the trial.

The detachable portion of the label located on each box of treatment was affixed to the 1st divider of the case report form.

The randomization codes were kept by the investigator in a sealed envelope.

The code could only be broken for a patient in the event of an SAE for which the investigator felt that he/she should know what the study product was in order to treat the event. In such a case, he/she had to contact the person in charge of the study before breaking the code.

A list of all the randomization codes was in the possession of the sponsor and the XXXXXX XXXXXX XXXXXX XXXXXX XXXXXX in XXXXXX

9.4.7. Prior and Concomitant Therapy

The prohibited prior treatments are listed in the exclusion criteria (section 9.3.3.).

The authorized concomitant treatments were:

- hypnotic agents (Zolpidem® or Stilnox®), if necessary, and anxiolytics (except for alprazolam) not to exceed 5 mg diazepam equivalent per day for a maximum duration of 5 days at the start of treatment,
- supportive psychotherapy (individual and/or family),
- long-term psychotherapy if it was already underway at the time of inclusion.

The prohibited concomitant treatments were:

- electroconvulsive therapy,
- SRIs and tricyclics, other than the study treatment,
- lithium, anticonvulsants, MAOIs, atypical antidepressants, amphetamine psychostimulants, anxiolytics (except for hypnotic agents, e.g. Zolpidem®), sedatives, neuroleptics, sumatriptan, long [term] corticosteroids or thyroxine, anticoagulants or ACE inhibitor antiarrhythmics.

9.4.8. Treatment Compliance

An assessment of compliance was performed by counting the drugs dispensed and those returned. In addition, a card for recording the counts was distributed to each investigator for completion by the patient. These cards were collected at the same time as the case report forms.

9.5. Efficacy and Safety Variables

9.5.1. Efficacy Assessment

9.5.1.1. Primary Efficacy Variable(s)

The primary efficacy criterion was based on the number of complete responders.
Complete response is defined as an improvement in the MADRS score of 50% or more compared with the baseline score at the enrollment visit.
It was assessed on D56, the end point of the evaluation.

- Clinical Global Impression (CGI) at D56:
  This score consists of the evaluation of:

  . the disease severity (normal to very seriously affected patient),

  . the global improvement of the disease (very much improved to very aggravated),

  . the efficacy index from 01 to 16 defined by the combination of 8 factors:

  - 4 related to therapeutic efficacy

  - 4 related to Adverse Effects

It is described in the following table:

ADVERSE EFFECTS ASSOCIATED WITH THE TREATMENT* / **THERAPEUTIC EFFICACY**	**NONE**	**MODERATE** No impact or slight impact on daily activities	**SIGNIFICANT** Having significant impact on daily activities	**VERY SIGNIFICANT** More significant than the therapeutic efficacy
MARKED - Very significant improvement. Complete remission of almost all symptoms.	01	02	03	04
MODERATE - Clear improvement. Partial remission of symptoms	05	06	07	08
MINIMAL - Slight improvement with little change to the patient's condition	09	10	11	12
NIL - Condition unchanged or aggravated	13	14	15	16

* Causality: possible or very probable, assessed by the investigator.

Indices 03, 04, 07, 08, 11, 12, 15 and 16 are treatment failures.
The evaluation was performed at D21, D56, D84, D112, D130, D158 and the last day of treatment in the event treatment was discontinued in between these visits.

9.5.1.2. Other efficacy criteria

- MADRS scale

The 10 items in the scale were assessed by the investigator and the global score was recorded at D-7, D1, D7, D21, D28, D42, D56 and the day the study ended.

- CDI scale

This self-report was completed by the patient during the same visits as for the MADRS scale, which it supplements.

The responses to the 27 questions were assigned a value of 0 (absent or normal) to 2 (severe). The total score was obtained by addition. The higher the score, the more pathological the condition.

- GAF:

A value corresponding to the psychological, social and occupational functioning constitutes the GAF score.
The lower the number, the more affected the patient is.
The GAF was performed during each visit from D1 to D56 and on the day the trial ended.

- HSCL 58 self-report:

This assesses the patient's condition by means of 58 items.
It was completed by the patient at D1, D21 and D56.
3 factors were studied and formed the subscores of this scale: inhibition-[psychomotor] retardation, depressed mood, neurovegetative [problems].

9.5.2. Safety Assessment

This assessment consists of recording all intercurrent events discovered during the history-taking and clinical examination or spontaneously reported by the patient or his/her parents at each visit.

Tolerance was assessed in all patients who took at least one dose of treatment.

The nature of each event, the date of onset, the duration, the severity and the relationship to the treatment were established by the investigator.

9.5.3. Appropriateness or Validity of Measurements

The scales for measuring the efficacy criteria are all validated standard techniques used in current practice to assess depression.

Defining a complete response by using the improvement in the MADRS score has also been validated and is commonly used in the assessment of depression.

9.6. Quality Assurance

This study was conducted in accordance with the French Good Clinical Practices and the Standard Operating Procedures of Laboratoires SmithKline Beecham.

The results of this study are confidential, and in this regard any written or oral scientific presentation of all or part of this study may not be made without the prior agreement of Laboratoires SmithKline Beecham.

During the trial, the CRAs paid regular visits to all of the investigators. The number of visits depended on the number of patients included at the centers. A copy of the visit reports is available.

In accordance with good clinical practices, the investigator[s] agreed to keep all documents relating to the study for a period of at least 15 years after it ended.

9.7. Statistical Methods

The plan for the statistical analysis was followed as specified in the protocol (Appendix 16.1.1). The analysis began with a description of the population at inclusion (D1) in order to verify the comparability of the two treatment groups, then continued with an analysis of the efficacy and safety criteria.

9.7.1. Statistical and Analytical Plan

The statistical analysis was performed by Société Biologie & Industrie using SAS software (version 6.12 for Windows; SAS Institute, North Carolina, USA).

The statistical tests were interpreted under two-tailed conditions and with the type I risk ζ set at 5% and the η-risk set at 20%.

For the quantitative variables, the mean, the standard deviation, the minimum and maximum values, the median and total number are provided by treatment group.

For the qualitative variables, the total number and the percentage are presented by treatment group.

The comparability of the 2 treatment groups at inclusion was verified using Student's t test for the quantitative variables and a chi-squared or a Fisher's exact test for the qualitative variables.

For the patients who withdrew from the study (regardless of the reason), the last available efficacy evaluations were carried forward to the end point of the evaluation in question. Thus the "last observation carried forward" (LOCF) method was applied to all of these patients in the primary analysis.
In addition, an "observed case" (OC) analysis was also performed.

The statistical analysis was performed for the ITT population and the PP population.

The statistical methods used to analyze the different efficacy criteria were the following:

For the first primary criterion:

- number of complete responders, defined as the number of patients who had a 50% or greater reduction in their MADRS between visit D56 and the D1 enrollment visit.
  The two treatment groups were first compared to the percentage of complete responders via the chi-squared test, then using logistic regression, taking into account the covariables of calculated age, MADRS values at inclusion, and center group.
  The odds ratio and the 95% confidence interval were calculated.

For the second primary criterion:

- the Clinical Global Impression (CGI) score at D56.
  The two treatment groups were compared using the Cochran-Mantel-Haenszel test, stratified by center group.

For the secondary criteria:

- change in the MADRS score at D7, D21, D42, and D56 compared with the enrollment visit, and change in the GAF for these same visits.
  A repeated measurement analysis was performed using the MADRS score at inclusion and the center groups as covariables.

For the following secondary criteria:

- The variations in the CGI criteria compared with the inclusion [values], the disease severity at D21 and D56 and the global improvement on D56. The analysis used the Wilcoxon nonparametric test.

- The number of early failures, defined as the need to discontinue the study treatment, change antidepressants or add another psychotropic agent before visit D56 due to a lack of clinical improvement, poor tolerance of the study treatment or a suicide attempt, was compared with the number of non-responders at D56 using the chi-squared test.

- The comparison of the HSCL 58 self-report scales in the two treatment groups, comparing both the total score and the inhibition-[psychomotor] retardation, depressed mood, and neurovegetative factors, based on the data observed, was performed using the Wilcoxon nonparametric test.

- The CDI self-rating scale was presented in a description.

A first analysis was performed of the total population and the center groups.

One of the centers that participated in the study differed from the rest, in that it was a suicide center, where [the condition of] the patients could be thought to be potentially more serious. An analysis was performed grouping all the centers versus this suicide center, as the latter alone recruited 23% of the patients.

A second analysis took into account the stratification by age bracket (12 to 15 years and 11 months for bracket I, and 16 to 20 years and 11 months for bracket II), which was planned for in the randomization. This was based on the same model as the first analysis.

Tolerance was analyzed in the following manner:

The analysis of intercurrent events consists of, by treatment group, by number of patients who presented with at least one Intercurrent Event, and by total number of Intercurrent Events for:
- the total number of events taken all together,
- the number of events that occurred during the first treatment phase (up to visit D21),
- the number of events that occurred during the dosage adjustment phase,
- the number of serious events declared to be severe by the investigator that were attributable (possible or probable) to the study product,
- the number of events that led to termination of the study.

The number of events was also presented according to the WHO classification (by "Body system" and "Preferred term").

Finally, a descriptive analysis of efficacy and safety was performed for the patients who continued treatment beyond D56.

9.7.2. Determination of sample size

The calculation of the number of subjects required for the comparison of the two study treatments on the basis of the primary efficacy criterion (number of complete responders) was based on the following data: the response rate with paroxetine in adolescent depression is approximately 75% (complete remission and improvement with residual symptoms) according to Rodriguez-Ramos et al. (Eur. Journal of clinical research, 1996; 8: 49-61). The mean response rate with tricyclics in adolescent depression (Hazell et al.: a meta-analysis, BMJ vol. 310, 1995, 897-900) is approximately 50% (50% nonimprovement on average for authors Boulos: 6/12, Hughes: 6/13, Puig-Antich: 9/16).

Thus the expected difference between the two treatments was 25%.

The number of subjects necessary was thus 104, or 52 per group.

In the knowledge that stratification by age bracket was envisioned, a minimum number of 30 patients per group and per age bracket was necessary, or 60 patients minimum per age bracket, i.e., 120 evaluable patients in all.
One hundred twenty-five patients were enrolled, and the analysis covered 121 patients (60 for bracket I and 61 for bracket II).

9.8. Changes in the Conduct of the Study

No major change occurred in the execution of the trial, other than taking into account amendment no. 3 and no. 4.

10 STUDY PATIENTS

10.1. Disposition of Patients

[10.1.1.] Distribution by center

Thirty-nine centers in France participated in this study, 24 of which (i.e. 61.5% of the centers) enrolled at least one patient. This is related to the difficulty of recruiting this type of adolescent, in whom the warning signs are extremely polymorphous. Furthermore, it should be pointed out that to our knowledge no previous study designed to compare two treatments had ever been conducted in France in such young adolescents and children (bracket I).

The complete list of centers that participated in the trial is presented in Appendix 16.1.4.

The distribution by center and by age bracket of the patients screened and enrolled is presented in the following table:

Table 1 Distribution by Center and Age Bracket of Patients Screened and Enrolled

Center no.	Investigator	Patients screened	Total no. of patients enrolled	Bracket 1	Bracket 2
1	xxxxxxx	5	3	1	2
2	xxxxxxx	5	5	3	2
4	xxxxxxx	2	1	1	0
7	xxxxxxx	28	28	14	14
8	xxxxxxx	7	7	3	4
9	xxxxxxx	2	2	1	1
10	xxxxxxx	1	1	0	1
11	xxxxxxx	11	11	5	6
14	xxxxxx	12	9	5	4
15	xxxxx	12	12	4	8
16	xxxxxx	5	5	4	1
17	xx xxxx	1	1	1	0
18	xxxxxx	2	2	1	1
20	xxxxx	3	3	2	1
21	xxxxx	1	1	1	0
22	xxxxxx	2	1	1	0
27	xxxxxx	10	9	0	9
29	xxxxxxx	7	7	7	0
32	xxxxxx	4	4	0	4
33	xxxxxxx	6	4	0	4
35	xxxxxxx	1	1	1	0
36	xxxxxxxx	4	4	4	0
37	xxxxxxx	1	1	1	0
38	xxxxxxx	3	3	3	0
39	xxxxxxx	1	0	0	0
Total		136	125	63	62

Thus eleven patients were selected but not enrolled because they did not meet the inclusion criteria.

The first patient was enrolled on 03/17/97 and the last patient was enrolled on 12/21/98; the enrollment period was therefore 21 months. The study (covering 56 days) ended on 02/16/99 for the last patient, and the total duration of the study was 23 months.

Of the 125 randomized patients, all of the patient records from center 36 (i.e. 4 patient records) were considered unusable because the data were unreliable. The discrepancies between the source records, case report forms, and patient diaries involved the visit dates, compliance with the wash-out period, and the date of the first dose. A narrative synopsis of these patient records is presented in the appendices. It summarizes the inconsistencies and discrepancies and the adverse events. These four patient records were not included in either the efficacy or the safety analysis.

Center no. 7 was a suicide center that recruited 23% of the usable population.

A total of 121 patient records were analyzed: 58 patients received Anafranil® and 63 received Deroxat®. The number of patients enrolled per treatment group and per center is presented in the following table:

Table 2 Distribution of Patients in the ITT Population by Center

Center	Anafranil® Group	Deroxat® Group	Total
1	2	1	3
2	2	3	5
4	1	0	1
7	14	14	28
8	3	4	7
9	2	0	2
10	0	1	1
11	6	5	11
14	4	5	9
15	6	6	12
16	2	3	5
17	0	1	1
18	0	2	2
20	1	2	3
21	0	1	1
22	0	1	1
27	5	4	9
29	4	3	7
32	2	2	4
33	2	2	4
35	1	0	1
37	0	1	1
38	1	2	3
1	2	1	3

Among the 121 analyzable patients, 60 patients were aged 12 to 16 years (minus one day), bracket I, and 61 were aged 16 years to 21 years [(minus one day)], bracket II.

10.1.2. Early terminations

The distribution of the population by treatment group and by [age] bracket is represented in the following figure:

Figure 1 Patient Distribution

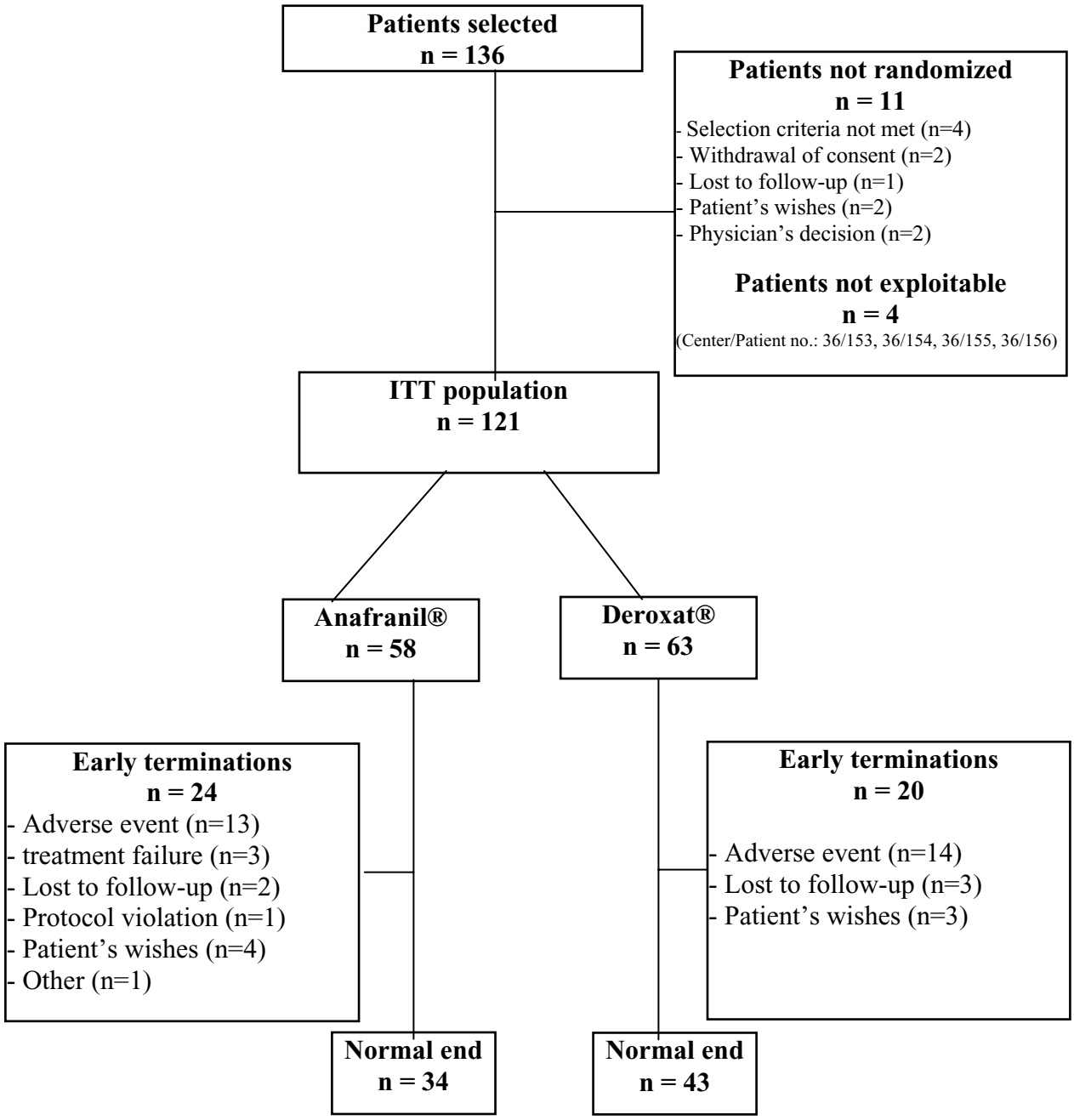


Figure 2 Distribution of Patients Aged 12 to 15 Years and 11 Months (Bracket I)

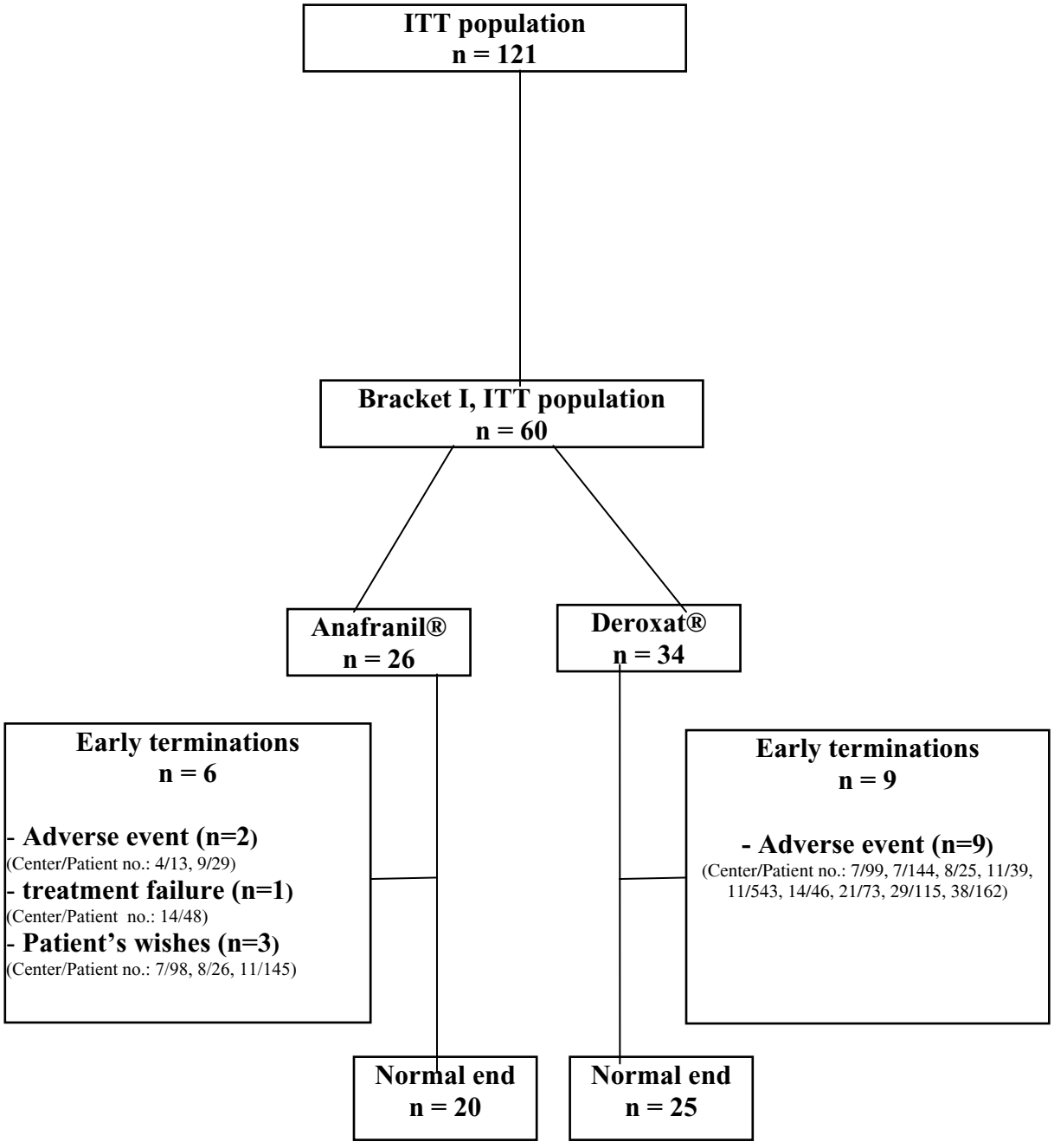
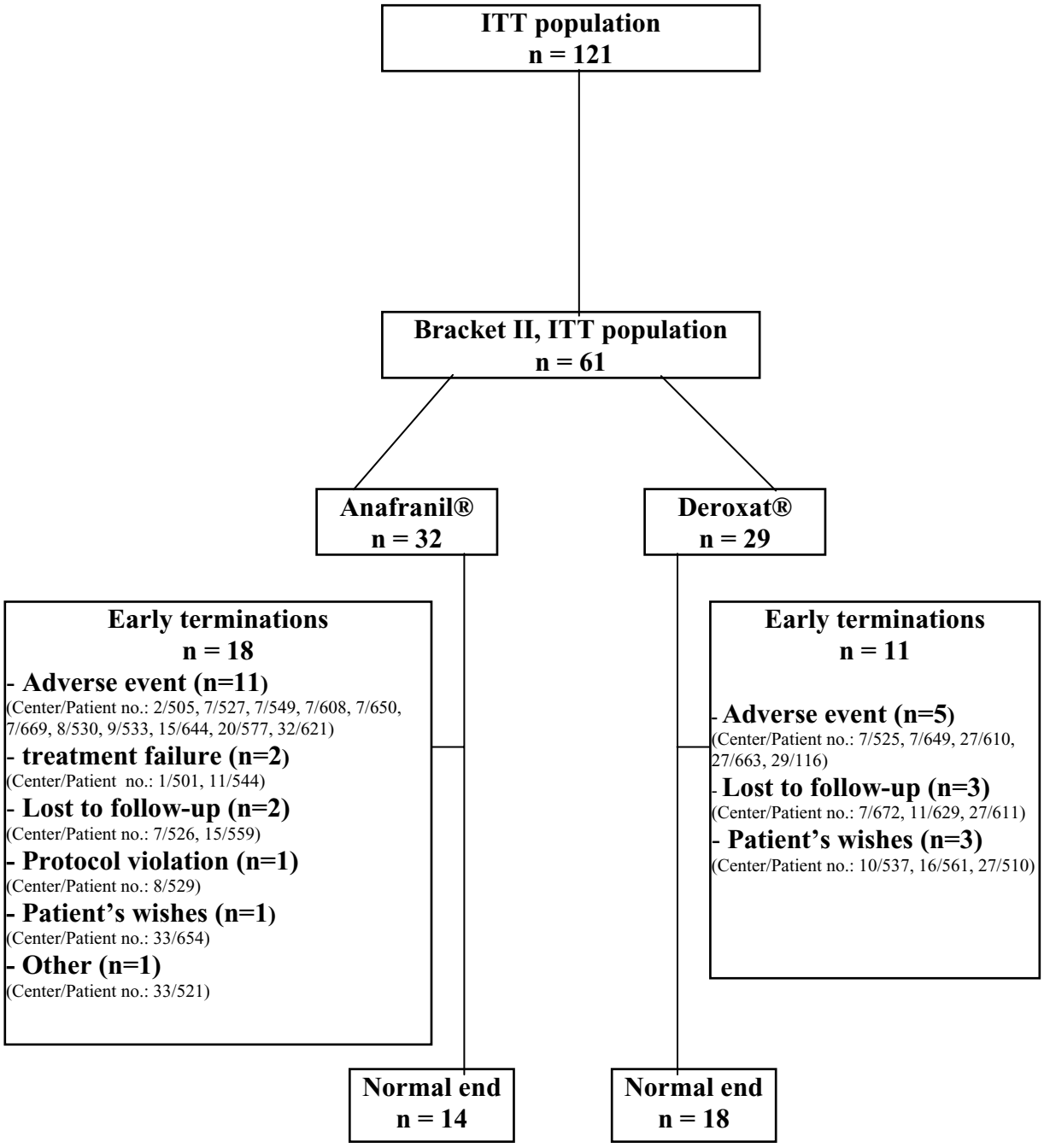


Figure 3 Distribution of Patients Aged 16 to 20 Years (Bracket II)



By reading the preceding figures, it can be seen that the early terminations are equivalent (p = 0.27) in the 2 treatment groups: 24 in the Anafranil® group, or 41.4%, versus 20 patients in the Deroxat® group, or 31.8%.

The main reason for the early terminations was the occurrence of an intercurrent event (61.4%), followed by terminations of the study at the request of the patients or their parents (15.9%), [and] patients lost to follow-up (11.4%); treatment failures represented only 6.8% of the reasons for termination. These were all (3 patients) in the Anafranil® group.

As for the terminations due to the occurrence of an intercurrent event, the distribution between the treatment groups was 54.2% in the Anafranil® group versus 70% in the Deroxat® group.
The mean duration of treatment of the patients who had an early termination, regardless of the reason, was 22.6 days (∂ 15.1) in the Anafranil® group versus 21.0 days (∂ 13.3) in the Deroxat® group, with no statistically significant difference between the 2 treatment groups (p = 0.59).

The ITT population included all patients who received at least one dose of the study treatment.
The PP population included the patients in the ITT population who did not have a major protocol deviation and who took their treatment for at least 21 days.
The mean duration of treatment was 49.7 days (± 17.1) for bracket I, and 40.6 days (± 21.6) for bracket II. For both bracket I and bracket II, there was no difference between the 2 treatment groups (p = 0.21 for bracket I and p = 0.33 for bracket II).

10.2. Protocol Deviations

Protocol deviations were examined for 121 patients in the ITT population (58 patients taking Anafranil®, 63 patients taking Deroxat®), and they break down as follows:

Table 3 Number of Protocol Deviations

PROTOCOL DEVIATIONS	Anafranil® Group	Deroxat® Group
Selection visit		
∉ Tanner stage I	3	-
∉ Weight less than 35 kg	1	-
∉ Exclusion criteria not complied with	-	1
Enrollment visit		
∉ Decrease of more than 20% in the MADRS compared with the selection visit	1	-
∉ Randomization not complied with (age bracket not complied with)	1 3	4 1
∉ Taking prohibited treatments prior to inclusion	-	-
During the study		
∉ Interval between visits not complied with	-	1
∉ Missed visits	1	1
∉ Failure to comply [with treatment] for 2 consecutive visits	1 10	1 16
∉ Taking prohibited treatments during the study	1	-
∉ Breaking of the blind*		
Duration of treatment less than 21 days	12	12

* see Table no. 13 [sic]

The patient distribution according to the type of deviation is as follows:

Table 4 Tanner Stage I

Anafranil® Group (n=3)		Deroxat® Group	
Center	Patient	Center	Patient
11	38		
11	134		
11	145		

Table 5 Weight Less than 35 kg

Anafranil® Group (n=1)			Deroxat® Group		
Center	Patient	Weight (kg)	Center	Patient	Weight (kg)
29	131	30			

Table 6 Exclusion Criterion Not Complied With

Anafranil® Group		Deroxat® Group (n=1)	
Center	Patient	Center	Patient
		7	525

This patient presented with intense suicidal ideation (criterion no. 5) and had a history of a suicide attempt in the month prior to inclusion (criterion no. 6).

Table 7 Decrease of More than 20% in the MADRS at the Enrollment Visit Compared with the MADRS at the Selection Visit

Anafranil® Group (n=1)		Deroxat® Group	
Center	Patient	Center	Patient
38	163		

MADRS D-7: 36 MADRS D1: 26 (MADRS D-7 - MADRS D1)/MADRS D-7 = 27.7%

The treatments were assigned with stratification by age bracket:

- theoretical bracket I = 12 years (144 months) to 15 years and 11 months (191 months): patient nos. 1 to 176
- theoretical bracket II = 16 years (192 months) to 20 years and 11 months (251 months): patient nos. 501 to 676

Table 8 Randomization Not Complied With

Anafranil® Group (n=1)			Deroxat® Group (n=4)		
Center	Patient	Actual age (months)	Center	Patient	Actual age (months)
38	163	236	29	116	194
			11	542	191
			11	543	175
			14	668	187

The stratification subsequently adopted was that calculated based on the patients' actual ages.

Table 9 Interval Between Visits Not Complied With

Anafranil® Group			Deroxat® Group (n=1)		
Center	Patient	Visits	Center	Patient	Visits
			1	638	D1, D7

Patient 638 came in for visit D7 three weeks after D1. Moreover, visit D7 took place when the patient was no longer taking the treatment. In fact, the patient's treatment had been interrupted for 15 days after the appearance of intercurrrent events (dry mouth, malaise and skin rash). The first event led to the discontinuation of treatment in this young woman, who was a flutist during the study period.

Table 10 Missed Visits

Anafranil® Group (n=1)			Deroxat® Group (n=1)		
Center	Patient	Missed visits	Center	Patient	Missed visits
38	163	D7, D28	15	557	D42, D56

Patient 557 made visits D42 and D56 by telephone.

Table 11 Failure to Comply [with Treatment] for 2 Consecutive Visits

Anafranil® Group (n=1)			Deroxat® Group (n=1)		
Center	Patient	Visits	Center	Patient	Visits
7	147	D42 & D56	7	528	D42 & D56

Table 12 Breaking of the Blind

Anafranil® Group (n=1)		Deroxat® Group	
Center	Patient	Center	Patient
20	577		

The blind was broken for patient 577 on May 27, 1997, when he had just attempted suicide. This patient had discontinued treatment that same day.

Table 13 Prohibited Prior Treatments

Anafranil® Group (n=3**)**

Center	**Patient**	**Prior treatment**	**Date of D1**	**Date treatment started**	**Date treatment ended**	**Duration in days**
7	97	Zopiclone	11/14/97	11/09/97	11/13/97	5
7	549	Cyamemazine	02/13/98	02/06/98	02/09/98	4
15	50	Levopromazine	02/12/98	02/03/98	02/12/98	10

Deroxat® Group (n=1)

Center	**Patient**	**Prior treatment**	**Date of D1**	**Date treatment started**	**Date treatment ended**	**Duration in days**
7	24	Zopiclone	11/13/97	11/09/97	11/13/97	5

Table 14 Prohibited Concomitant Treatments

Anafranil® Group (n=10)

Center	Patient	Concomitant treatment	Date of D1	Date of last dose or D56	Date concomitant treatment started	Date concomitant treatment ended	Duration in days
7	17	Diazepam	05/19/98	07/21/98	06/02/98	06/11/98	10
		Clorazepate dipotassium			05/19/98	05/24/98	6
7	21	Alprazolam	05/16/97	07/10/97	05/18/97	05/19/97	2
		Alprazolam			05/20/97	05/21/97	2
		Alprazolam			05/22/97	06/03/97	13
		Zopiclone			05/21/97	05/21/97	1
		Alprazolam			05/17/97	05/17/97	1
7	147	Alprazolam	10/31/98	12/29/98	12/01/98	Continuing	>29
7	527	Bromazepam	06/09/97	06/21/97	06/19/97	06/23/97	5
7	606	Bromazepam	12/08/97	02/02/98	12/29/97	Continuing	>36
7	608	Alprazolam	02/06/98	03/10/98	01/30/98	Continuing	>40
8	529	Diazepam	04/12/97	05/16/97	04/16/97	04/17/97	2
		Diazepam			04/27/97	04/27/97	1
		Diazepam			05/13/97	05/13/97	1
11	544	Betamethasone	02/04/98	03/18/98	03/02/98	03/06/98	5
15	49	Bromazepam	12/29/97	02/24/98	01/29/98	02/02/98	5
15	641	Prazepam	11/09/98	01/04/99	11/10/98	11/16/98	7

Deroxat® Group (n=16)

Center	Patient	Concomitant treatment	Date of D1	Date of last dose or D56	Date concomitant treatment started	Date concomitant treatment ended	Duration in days
7	23	Alprazolam	09/03/97	10/28/97	09/30/97	10/30/97	31
7	24	Alprazolam	11/13/97	10/07/98	11/07/97	Continuing	>60
7	99	Bromazepam	03/06/98	04/20/98	02/28/98	04/16/98	47
		Alprazolam			04/16/98	Continuing	>5
7	100	Diazepam	05/14/98	07/08/98	05/14/98	06/09/98	27
7	144	Diazepam	10/24/98	10/30/98	10/17/98	11/30/98	45
7	525	Alprazolam	05/27/97	06/05/97	05/28/97	06/06/97	10
		Valpromide			05/23/97	06/04/97	13
		Valpromide			06/05/97	06/06/97	2
		Amisulpride			06/03/97	06/04/97	2
		Amisulpride			06/05/97	06/06/97	2
7	528	Amisulpride	08/30/97	10/24/97	08/26/97	09/09/97	15
7	607	Bromazepam	01/15/98	03/12/98	01/10/98	03/12/98	62
7	649	Alprazolam	11/16/98	12/03/98	11/23/98	11/29/98	7
7	670	Diazepam	09/22/98	11/17/98	09/25/98	09/28/98	4
8	25	Clorazepam	10/14/97	10/21/97	10/19/97	10/19/97	1
		Levomeprazine			10/19/97	10/19/97	1
11	37	Hydrocortisone butyrate	05/26/97	07/22/97	06/15/97	06/15/97	1
14	47	Loxapine succinate	08/09/97	10/04/97	09/26/97	09/26/97	1
21	73	Cyamemazine	02/09/98	03/05/98	02/06/98	03/03/98	26
37	165	Alprazolam	10/07/98	12/09/98	10/11/98	10/11/98	1
		Alprazolam			12/07/98	12/07/98	1
38	162	Bromazepam	12/22/98	01/30/99	01/13/99	01/20/99	8
		Bromazepam			01/20/99	02/01/99	13

Table 15 Duration of Treatment Less than 21 Days

Anafranil® Group (n=12)			Deroxat® Group (n=12)		
Center	Patient	Duration (days)	Center	Patient	Duration (days)
1	501	14	7	144	7
2	505	15	7	525	10
4	13	3	7	649	18
7	527	12	8	25	8
7	549	11	10	537	5
7	650	6	11	39	16
9	29	15	11	629	12
9	533	6	14	46	11
15	559	9	27	610	2
22	654	8	27	663	18
32	621	3	29	115	19
33	521	9	29	116	20

The duration of treatment was calculated based on the dates of the first and last dose of treatment, and does not take into account temporary interruptions of treatment during the study.

After consulting with Laboratoires SmithKline Beecham and in agreement with the investigators-coordinators at a meeting while the blind was still in place, major and minor protocol deviations were defined as follows:

Definition of major and minor deviations

Minor deviations
- Tanner stage equal to 1,
- weight less than 35 kg,
- randomization not complied with.

Major deviations
- interval between visits not complied with,
- missed visits,
- failure to comply [with treatment] for 2 consecutive visits,
- breaking of the blind, (1)
- duration of treatment less than 21 days.

Special cases
- exclusion criterion not complied with,
- decrease of more than 20% in the MADRS compared with the selection visit,
- prohibited previous and/or concomitant treatments. (2)

1) The blind was broken the day the last dose of treatment was taken. Nevertheless, the final evaluation (early withdrawal) was performed 3 days after the blind was broken.
2) The major or minor deviation status for patients who took prohibited prior and/or concomitant treatments was determined based on the number of prohibited treatments taken, the number of days the prohibited treatment was taken, the period it was taken, and the type of treatment.

Patients not included in the PP population

In all, 42 patients were not included in the PP analysis.

Table 16 Patients Exhibiting Major Deviations

Anafranil® Group (n=20)

Center	Patient	Reason
1	501	Duration of treatment less than 21 days
2	505	Duration of treatment less than 21 days
4	13	Duration of treatment less than 21 days
7	17	Prohibited concomitant treatment
7	21	Prohibited concomitant treatment
7	147	Failure to comply [with treatment] for 2 consecutive visits + Prohibited concomitant treatment
7	527	Duration of treatment less than 21 days
7	549	Duration of treatment less than 21 days
7	606	Prohibited concomitant treatment
7	608	Prohibited concomitant treatment
7	650	Duration of treatment less than 21 days
9	29	Duration of treatment less than 21 days
9	533	Duration of treatment less than 21 days
15	50	Prohibited previous treatment
15	559	Duration of treatment less than 21 days
20	577	Breaking of the blind
22	654	Duration of treatment less than 21 days
32	621	Duration of treatment less than 21 days
33	521	Duration of treatment less than 21 days
38	163	Visits D7 and D28 missed, MADRS criterion not complied with

Deroxat® Group (n = 22)

Center	Patient	Reason
1	638	Interval between visits not complied with
7	23	Prohibited concomitant treatment
7	24	Prohibited previous and concomitant treatment
7	99	Prohibited concomitant treatment
7	100	Prohibited concomitant treatment
7	144	Duration of treatment less than 21 days + Prohibited concomitant treatment
7	525	Duration of treatment less than 21 days + Prohibited concomitant treatment
7	528	Failure to comply [with treatment] for 2 consecutive visits + Prohibited concomitant treatment
7	607	Prohibited concomitant treatment
7	649	Duration of treatment less than 21 days + Prohibited concomitant treatment
8	25	Duration of treatment less than 21 days + Prohibited concomitant treatment
10	537	Duration of treatment less than 21 days
11	39	Duration of treatment less than 21 days
11	629	Duration of treatment less than 21 days
14	46	Duration of treatment less than 21 days
15	557	Visits D42 and D56 missed
21	73	Prohibited concomitant treatment
27	610	Duration of treatment less than 21 days
27	663	Duration of treatment less than 21 days
29	115	Duration of treatment less than 21 days
29	116	Duration of treatment less than 21 days
38	162	Prohibited concomitant treatment

In conclusion, the PP population consisted of 79 patients, or 38 patients taking Anafranil® and 41 patients taking Deroxat®.

11 EFFICACY EVALUATION

11.1. Data Sets Analyzed

The ITT population consisted of 121 patients, 58 in the Anafranil® group and 63 in the Deroxat® group.
Demographic characteristics and other data at inclusion were analyzed in these 121 patients.
The PP population consisted of 79 patients, 38 in the Anafranil® group (or 60% of the ITT patients who could be analyzed) and 41 in the Deroxat® group (or 65% of the ITT patients who could be analyzed).

All data appearing in the protocol and case report forms were analyzed, and are detailed in Appendix 14.

26 patients (9 in the Anafranil® group and 17 in the Deroxat® group) continued study treatment beyond D56, and 8 patients (5 in the Anafranil® group and 3 in the Deroxat® group) ended the study at D168. The efficacy evaluation for this period was a descriptive evaluation and is detailed in Appendix 14.

11.2. Demographic and Other Baseline Characteristics

11.2.1. Demographic characteristics

Demographics are given in the following table:

Table 17 Demographic Characteristics

		Anafranil® Group	Deroxat® Group	p Value
Sex	M	19, or 32.8%	29, or 46.0%	0.14
	F	39, or 67.2%	34, or 54.0%	
Age (years)	n	58	63	
	m	16.2	15.9	
	sd	2.2	2.0	0.54
	min	12.2	12.1	
	max	19.8	20.6	
Height (cm)	n	58	63	
	m	163.7	166.7	
	sd	9.1	8.8	0.07
	min	133	145	
	max	183	183	
Weight	n	58	63	
	m	54.2	56.8	
	sd	11.2	13.0	0.25
	min	30	36	
	max	90	95	

There were no differences between the 2 treatment groups for any of these parameters. However, there was a predominance of females in the Anafranil® group.

11.2.2. Medical and surgical history.

39 patients in the Anafranil® group (or 67.2%) versus 41 patients in the Deroxat® group (or 65.1%) presented with at least one past medical event or pathology. There was no statistically significant difference between the 2 treatment groups (p = 0.80). The most commonly observed pathologies were, in decreasing order:

Table 18 Most Common Associated Pathologies

Type of medical event	Anafranil® n	Deroxat® n
ENT	14	14
Dermatological	13	14
GI	11	12
Genital/Urinary	8	6
Respiratory	8	8

The type of previous medical events mentioned corresponded with the average age of the population.

11.2.3. Disease history

This was the first depressive episode for 18 patients in the Anafranil® group (31.0%) versus 24 patients (38.1%). There was no difference between the 2 treatment groups for this parameter (p = 0.42).

Of the 42 patients who presented with prior episodes, the number of episodes was equivalent in both treatment groups (p = 0.93); 70.6% of the Anafranil® group presented with a prior episode versus 73.7% of the Deroxat® group.
17.7% of patients in the Anafranil ® group versus 15.8% in the Deroxat® group presented with 2 prior episodes.

Six patients were in psychotherapy, 3 in each group.

The manner in which care had been sought was comparable in the 2 treatment groups (p = 0.98): one-quarter of patients presented to healthcare providers in emergency situations, 20% were sent by their treating physician, and slightly less than 40% were sent by their families.

11.2.4. History of suicide attempts

37.2% of patients in the entire population had a history of suicide attempts (37.9% in the Anafranil® group versus 36.5% in the Deroxat® group.).

However, the percentages of suicide attempts in the suicide center was 67.9% for all patients, with a different distribution between the Anafranil® (78.6%) and Deroxat® (57.1%) groups, although there is still no statistically significant difference.

Of the 45 patients who presented with a suicide attempt, 46.7% had made one attempt, 26.7% had made 2 attempts, 11.1% had made 3 attempts, and 15.6% had made 4 to 6 suicide attempts.

11.2.5. Characteristics of the depression at inclusion.

Disease Severity

The results for this parameter are given in the following table.

Table 19 Disease Severity at D1

Patient Status	Anafranil®	Deroxat®	p Value
Moderately ill	9, or 15.5%	3, or 4.8%	0.19
Markedly ill	34, or 58.6%	37, or 58.7%	
Severely ill	14, or 24.1%	20, or 31.8%	
Very seriously ill	1, or 1.7%	3, or 4.8%	

There was no statistically significant difference between the 2 treatment groups.

MADRS

MADRS scores were assessed at screening and inclusion. Inclusion values are given in the following table:

Table 20 MADRS at D1

MADRS	Anafranil®	Deroxat®	p Value
n	58	63	0.06
m	30.9	32.7	
sd	3.9	5.1	
min	24	24	
max	41	43	

There was no difference between the 2 treatment groups. When the results from the suicide center are compared to those from other centers, they are completely comparable and equivalent.

Other Scales

The results from the Hamilton Depression Scale and the GAF are given in the following table:

Table 21 Hamilton and GAF Scales at D1

		Anafranil®	Deroxat®	p Value
Hamilton dépression	n	57	63	0.34
	m	22.9	24.1	
	sd	4.1	5.4	
	min	13	12	
	max	33	37	
Current GAF	n	58	63	0.16
	m	46.9	44.8	
	sd	8.1	9.3	
	min	31	25	
	max	65	70	

There were no differences between the 2 treatment groups in any of these parameters.

11.2.6. Conclusion regarding demographic and disease history parameters

The patients included in the 2 treatment groups for this study were completely similar. There were no statistically significant differences between the 2 treatment groups for any of the variables studied.

The average of the general population was 16.1 years (± 2.1), 60% of whom were girls. This was the first depressive episode for 1/3 of the cases.

Of patients who had had a prior depressive episode, 72.2% had only experienced one.

37.2% of patients had thought about attempting suicide. The average MADRS score at inclusion was 32.

These patients were therefore representative of depression in adolescents, both in the characteristics of their depression and in the ratio of males/females.

11.3. Treatment Compliance

28 patients reported compliance below 80% at least once between visits D1 and D7, D7 and D21, D21 and D42, D42 and D56.
This information did not allow us compile figures on temporary discontinuation of treatment. Only compliance below 80% for 2 consecutive visits was considered as a major deviation from the protocol.

At D21 there were 22 instances where the dose was doubled, 13 in the Anafranil® group and 9 in the Deroxat® group. There were 16 instances where the dose was doubled in bracket I, or 30.2% of the patients in that bracket, and 6 in bracket II (or 13.6%).

The average dose per kg prescribed at D1 was 1.44 mg/kg in the Anafranil® group, with extreme values of 0.83 and 2.50. The average dose was 0.37 mg/kg in the Deroxat® group, with extremes of 0.21 and 0.56 mg/kg.

Although it initially appears that the Anafranil® dose was higher for the children in bracket I, it is interesting to note that 30% of the children in that bracket had their dosage doubled, whereas this was only true for 1 of 14 in bracket II (adolescents).

11.4. Analysis of Efficacy

The LOCF method was applied to all patients who did not complete the entire study, i.e. at D56.

Primary Criterion

11.4.1.1 Number of complete responders

The primary criterion was defined by the number of complete responders: those with a 50% improvement in the MADRS score compared with the baseline score at the enrollment visit.

The results for this parameter are given in the following table:

Table 22 Number of Responders at D56

	Anafranil®	**Deroxat®**	**p Value**
Number of Complete Responders	28, or 48.3%	41, or 65.1%	0.06

Although the p value is not significant, note that 65.1% of patients receiving Deroxat® were complete responders, versus 48.3% in the Anafranil® group.

If we compare the results from all centers to those from the suicide center, 47.7% were responders in the Anafranil® group, versus 69.4% in the Deroxat® group for all centers.
The results in the suicide center were completely equivalent: 50% in each treatment group. There was no center effect for the "number of responders" parameter.

The results concerning the improvements in MADRS values between D1 and D56 at the last visit are given in the following table:

Table 23 Percentage Reduction in MADRS at D56/D1

		Anafranil®	**Deroxat®**
MADRS (D1 – D56) % D1	n	58	63
	m	45	54
	sd	32	30
	min	-12	-31
	max	100	100

11.4.1.2 Global improvement and disease severity

114 patients showed improvement at the D56 assessment: 55 in the Anafranil® group and 59 in the Deroxat® group.

The improvement percentages are completely comparable (p = 0.71).

-Percentage of patients very much improved: 32.7% in the Anafranil® group and 33.9% in the Deroxat® group;
-Percentage of patients much improved: 25% in both treatment groups;
-Percentage of patients moderately improved: 18.2 in the Anafranil® group and 23.7% in the Deroxat® group;
-No change: 16.4% in the Anafranil® group and 8.5% in the Deroxat® group.

The conditions of 3 patients in the Anafranil® group and 5 in the Deroxat® group worsened during the study.

There was no difference in the global improvement results at D21 for the 2 groups (p = 0.73):

- 13.2% of patients were very much improved at D21,
- 30.7% were much improved,
- 32.5% were moderately improved,
- 12.3% saw no change,
- and 12 patients (10.5%) saw their conditions worsen (7 in the Anafranil® group and 5 in the Deroxat® group).

There was no statistically significant difference between the 2 treatment groups (p = 0.39) for a difference in disease severity between D1 and D56.

At D21, the results of the analysis of severity were the same as those for D56 (p = 0.59). In total, at D21, 79 patients saw a decrease in the severity of their condition versus 31 patients who saw no change, and 4 whose conditions worsened.

The figures are given in the following table, and incorporate the center effect:

Table 24 Percentage Reduction in MADRS at D56/D1, by Center Groups

MADRS (D1 – D56) % D1		**Anafranil®**	**Deroxat®**
All centers Without center 7	n m sd min max	44 46 33 -12 100	49 57 31 -31 100
Center 7 (suicide study)	n m sd min max	14 42 30 3 84	14 43 25 -3 75

For the primary criterion, the 2 groups were compared using logistic regression with these covariables: calculated age, MADRS value at inclusion, center group.

There was a statistically significant difference (p = 0.026) between the 2 treatment groups in favor of Deroxat®, and an effect of the MADRS score at inclusion (p = 0.03).
Improvement was greater in the Deroxat® group, and more so when the inclusion value was higher. In this model, age did not affect response to treatment.

The odds ratio of 2.42 means that for patients taking Deroxat®, the complete responder/non-responder ratio is approximately two and one-half times greater than that of patients taking Anafranil®, with a confidence interval of between 1.11 and 5.26.

11.4.2. Secondary criteria

11.4.2.1. Evolution of MADRS over time.

Table 25 Assessment of MADRS Over Time

MADRS		**Anafranil®**	**Deroxat®**
D1	n	58	63
	m	30.9	32.7
	sd	3.9	5.1
	min	24	24
	max	41	43
D7	n	58	63
	m	25.6	26.0
	sd	6.9	6.7
	min	2	2
	max	41	42
D21	n	58	63
	m	21.3	20.0
	sd	10.3	9.3
	min	1	2
	max	41	41
D28	n	58	63
	m	19.6	17.4
	sd	9.7	9.8
	min	3	2
	max	41	35
D42	n	58	63
	m	18.3	16.1
	sd	10.7	9.4
	min	0	0
	max	41	35
D56	n	58	63
	m	17.6	14.9
	sd	11.3	9.7
	min	0	0
	max	41	35

The repeated measures analysis of variance revealed a treatment group effect in favor of Deroxat® (p = 0.003). The decrease in the MADRS was greater over time in the Deroxat® group than in the Anafranil® group.

A MADRS effects was also found at inclusion ($p = 10^{-4}$).

These results are in favor of Deroxat® overall, but are difficult to interpret as the patients leaving the study, 44 in total or 36.4% of the population, had their last MADRS value carried forward to the end of the study, although 2/3 of them withdrew from the study for tolerance reasons.

11.4.2.2. GAF

GAF values are given in the following table:

Table 26 Evolution of GAF Over Time

GAF Value		**Anafranil®**	**Deroxat®**
D1	n	58	63
	m	46.9	44.8
	sd	8.1	9.3
	min	31	25
	max	65	70
D7	n	58	63
	m	52.8	51.4
	sd	10.5	10.7
	min	31	26
	max	90	75
D21	n	58	63
	m	57.3	56.1
	sd	13.9	14.4
	min	31	25
	max	85	81
D28	n	58	63
	m	59.3	59.8
	sd	15.0	15.8
	min	31	25
	max	90	90
D42	n	58	63
	m	61.6	62.0
	sd	15.1	16.9
	min	31	25
	max	85	90
D56	n	58	63
	m	63.5	63.5
	sd	16.3	17.5
	min	31	25
	max	90	90

The analysis of variance did not demonstrate a treatment effect ($p = 0.57$). The GAF values increased in both treatment groups over time, confirming previous results: the patients' states improve in psychological, social, and occupational functioning.

11.4.2.3 HSCL 58

No difference in the HSCL 58 scale was found between the 2 treatment groups, either at D21 (p = 0.47) or D56 (p = 0.55).

The graphs below show the evolution of this scale at the various visits, both in global score and in the 3 factors.

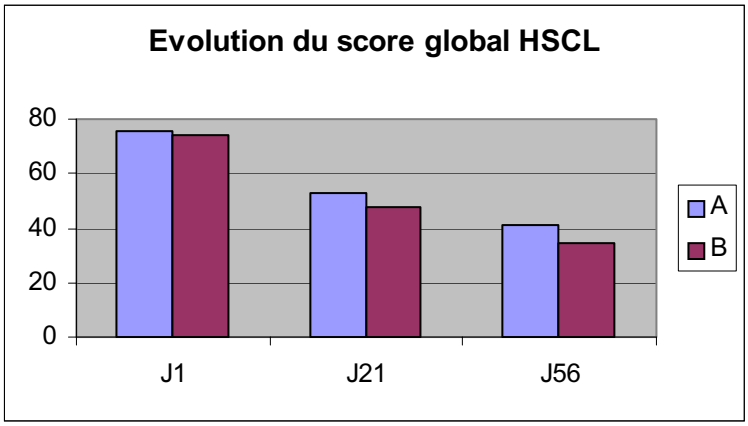


Figure 4: Evolution of Global HSCL Score

Figure 5: Evolution of the HSCL Inhibition-[Psychomotor] Retardation Factor

Items: 9, 14, 28, 32, 51, 55 , 56

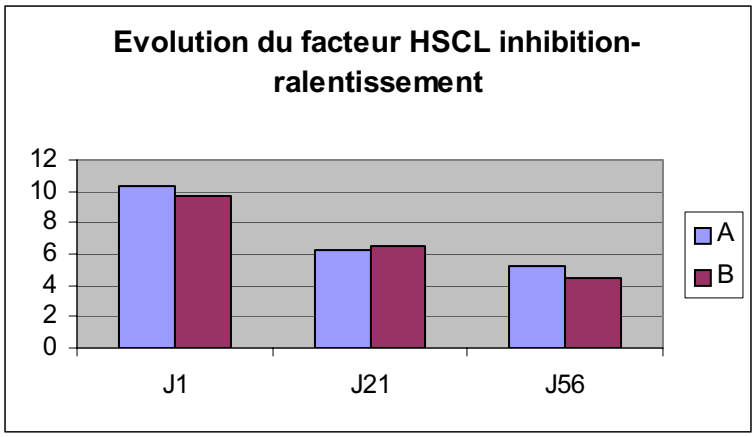


Figure 6: Evolution of the HSCL Depressive Mood Factor

Items: 15, 22, 29, 30, 31, 54

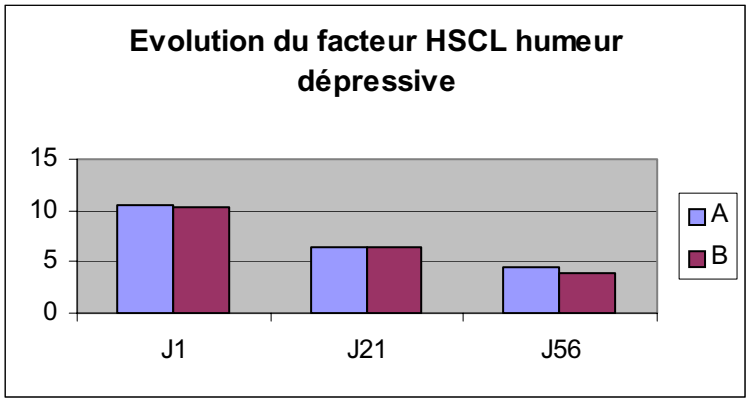
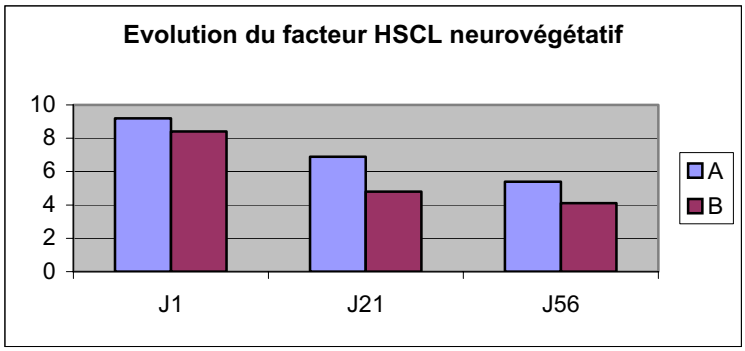


Figure 7: Evolution of the HSCL Neurovegetative Factor
Items: 2, 12, 15, 16, 17, 39, 40, 42



11.4.2.4. Early failures

Early failures, as defined in section 9.7, did not demonstrate a difference between the 2 treatment groups (p = 0.27); 23 patients, or 39.7%, in the Anafranil® group were considered early failures versus 19, or 30.2%, in the Deroxat® group.

There were 10 non-responders;: 7, or 12.1%, in the Anafranil® group, versus 3, or 4.8%, in the Deroxat® group.
Here again there was no statistically significant difference between the 2 treatment groups (p = 0.19).

11.5. Analysis of ITT Population, by Age Bracket

11.5.1. Demographic characteristics

The LOCF method was applied to all patients who did not complete the entire study, i.e. to D56. Recall that 2 age brackets had been defined at inclusion:

- Bracket I: from 12 years to 15 years 11 months,
- Bracket II: from 16 years to 20 years 11 months.

There was no statistically significant difference between the 2 treatment groups regarding age, weight and height parameters for either Bracket I or Bracket II.

However, there was a statistically significant difference between the 2 treatment groups (p = 0.03) regarding sex, with 8 male children in the Anafranil® group versus 20 in the Deroxat® group.
There was a predominance of females in Bracket II (65.6% in the Anafranil® group versus 69.0% in the Deroxat® group), but this was not statistically significant.

There was no statistical difference between the 2 treatment groups regarding suicide attempt history parameters, meaning ideation in previous depressive episodes, for either bracket I or bracket II.

Depressive episodes were found in 40.9% of patients in Bracket II versus 28.3% of patients in Bracket I.

35% of patients in Bracket I and 39.3% of patients in Bracket II presented with a history of suicide attempts.

Table 27 MADRS at Inclusion, by Age Bracket

		Anafranil®	Deroxat®	p Value
Bracket I	n	26	34	
	m	30.3	32.7	
	sd	4.1	5.2	0.08
	min	25	24	
	max	40	43	
Bracket II	n	32	29	
	m	31.4	32.7	
	sd	3.8	5.1	0.37
	min	24	25	
	max	41	43	

There was no difference between the 2 treatment groups in either bracket. The average MADRS scores were completely comparable in both brackets.

11.5.2. Early terminations

Recall that 44 patients terminated the study early, 24 in the Anafranil® group, and 20 in the Deroxat® group.

The results by bracket are as follows:

Table 28 Number of Early Terminations, by Age Bracket

	Anafranil®	**Deroxat®**	**p Value**
Bracket I	6/26	9/34	0.76
Bracket II	18/32	11/29	0.15

The reasons for early termination were:

Bracket I:
intercurrent event: 2 in the Anafranil® group
9 in the Deroxat® group.
- treatment failure: 1 in the Anafranil® group
- terminated by parents: 3 in the Anafranil® group

Bracket II:
intercurrent event: 11 in the Anafranil® group
5 in the Deroxat® group.
- treatment failure: 2 in the Anafranil® group
- lost to follow-up: 2 in the Anafranil® group
3 in the Deroxat® group.
- protocol violation: 1 in the Anafranil® group
- terminated by parents or patients: 1 in the Anafranil® group
3 in the Deroxat® group.
- other reasons: 1 in the Anafranil® group

1.5.3 Efficacy Analysis of the Primary Criterion

11.5.3.1 Complete Responders

The primary criterion was defined by the number of complete responders: a 50% improvement in the MADRS score over the baseline score at the enrollment visit.

The results for this parameter are presented by treatment group and by age bracket in the following table:

Table 29 Number of Responders by Age Bracket

Number of Complete Responders	**Anafranil®**	**Deroxat®**	**p Value**
Bracket I	15, or 57.7%	18, or 52.9%	0.71
Bracket II	13, or 40.6%	23, or 79.3%	0.002

There was a statistically significant difference in favor of Deroxat® (p = 0.002) in Bracket II. However, the percentage of responders are completely equivalent in the younger children.
One factor explaining this difference might be the dosages used: Anafranil® 75 mg and Deroxat® 20 mg for the first three weeks.

The Anafranil® dose may be considered low given the severity of the depressive episodes (MADRS value), but it is the dose used in practice and in a pharmacologically prudent approach. The Anafranil® dose was discussed at length with the investigators in order to minimize the risk for these young patients.

The results concerning the improvements in MADRS values between D1 and D56 or the last visit are given in the following table:

Table 30 Percentage Reduction in MADRS at D56/D1 by Age Bracket

MADRS (D1 – D56) % D1		**Anafranil®**	**Deroxat®**
Bracket I	n	26	34
	m	53	50
	sd	29	29
	min	0	-17
	max	93	100
Bracket II	n	32	29
	m	38	59
	sd	33	30
	min	-12	-31
	max	100	97

Logistic regression analysis was performed as above for the ITT population, removing age as a covariable.

There was no statistically significant difference between the 2 treatment groups for Bracket I. There was a statistically significant difference (p = 0.001) between the 2 treatment groups in favor of Deroxat® for Bracket II.

The odds ratio of 10.55 means that for patients in Bracket II taking Deroxat®, the responder/non-responder ratio was approximately ten and one-half times greater than that of patients taking Anafranil®, with a confidence interval of between 2.58 and 43.21.

11.5.3.2 Global Improvement (CGI)

114 patients showed improvement at the D56 assessment:

The improvement percentages were completely comparable (p = 0.07 in bracket I and p = 0.45 in bracket II).

114 patients showed improvement at the D21 assessment.

Likewise, the results of global improvement at D21 were no different in Bracket I (p = 0.69) or Bracket II (p = 0.74).

Table 31 Assessment of MADRS Over Time, by Bracket

MADRS		Anafranil®		Deroxat®	
		Bracket I	Bracket II	Bracket I	Bracket II
D1	n	26	32	34	29
	m	30.3	31.4	32.7	32.7
	sd	4.1	3.8	5.2	5.1
	min	25	24	24	25
	max	40	41	43	43
D7	n	26	32	34	29
	m	24.2	26.7	26.2	25.7
	sd	6.1	7.4	6.4	7.0
	min	11	2	13	2
	max	34	41	40	42
D21	n	26	32	34	29
	m	21.0	21.5	21.4	18.4
	sd	10.3	10.3	9.6	8.8
	min	6	1	4	2
	max	39	41	41	37
D28	n	26	32	34	29
	m	17.1	21.7	19.2	15.4
	sd	8.6	10.3	9.1	10.3
	min	4	3	2	2
	max	32	41	35	35
D42	n	26	32	34	29
	m	16.0	20.2	17.5	14.6
	sd	9.2	11.5	9.3	9.4
	min	4	0	0	2
	max	40	41	35	34
D56	n	26	32	34	29
	m	14.5	20.1	16.1	13.4
	sd	9.9	12.0	9.8	9.6
	min	2	0	0	1
	max	40	41	35	34

11.6. Per Protocol Analysis

The LOCF method was applied to all patients who did not complete the entire study, i.e. at D56. The PP population was 79 patients, 38 in the Anafranil® group and 41 in the Deroxat® group. Only the MADRS results are detailed.

11.6.1 Primary criterion

The primary criterion was defined by the number of complete responders, that is a 50% improvement in the MADRS score over the baseline score at the enrollment visit.

The results for this parameter are given in the following table:

Table 32 Number of Complete Responders, Per Protocol Population

	Anafranil®	**Deroxat®**	**p Value**
Number of Complete Responders	22, or 57.9%	34, or 82.9%	0.01

Tthere was a statistically significant difference in favor of Deroxat® (p = 0.01) by age bracket. The complete responders are given in the following table:

Table 33 Number of Complete Responders by Age Bracket, Per Protocol Population

	Anafranil®	**Deroxat®**	**p Value**
Bracket I	55.0%	73.9%	0.19
Bracket II	61.1%	94.4%	0.04

The difference between the 2 treatments was not significant in the younger children but was significant in the adolescents (p = 0.04), with an almost complete response in the Deroxat® group of patients.

The results of the improvement in MADRS values between D1 and D56 at the last visit are given in the following table:

Table 34 Percentage Reduction in MADRS, Per Protocol Population

		Anafranil®	**Deroxat®**
MADRS (D1 – D56) % D1	n	38	41
	m	54	65
	sd	29	24
	min	-3	-31
	max	100	100

The figures that take the centers into account are given in the following table:

Table 35 Percentage Reduction in MADRS, Per Protocol Population, by Center Groups

MADRS (D1 – D56) / D1 %		**Anafranil®**	**Deroxat®**
All centers Except center 7	n	32	36
	m	55	65
	sd	29	26
	min	-3	-31
	max	100	100
Center 7 (suicide study)	n	6	5
	m	47	60
	sd	33	9
	min	10	53
	max	84	74

For the primary criterion, the 2 groups were compared using logistic regression with these covariables: calculated age, MADRS value at inclusion, center groups without covariable interaction.
There was a statistically significant difference ($p = 0.018$) between the 2 treatment groups.
Improvement was greater in the Deroxat® group. In this model, age did not affect response to treatment.

The odds ratio of 3.67 means that for patients taking Deroxat®, the responder/non-responder ratio is approximately three and one-half times greater than that of patients taking Anafranil®, with a confidence interval of between 1.25 and 10.82.

Logistical regression by age bracket demonstrated a treatment group effect (Bracket II) in adolescents ($p = 0.001$).

The percentages for the MADRS reduction by age bracket were completely comparable (see Appendix Table 112).

11.6.2 Secondary criteria

MADRS assessment over time.

Table 36 Evolution of MADRS Over Time, Per Protocol Population

MADRS		**Anafranil®**	**Deroxat®**
D1	n	58	63
	m	30.9	32.7
	sd	3.9	5.1
	min	24	24
	max	41	43
D7	n	38	41
	m	24.5	25.1
	sd	6.8	5.7
	min	2	13
	max	34	42
D21	n	38	41
	m	17.8	17.7
	sd	9.4	8.7
	min	1	4
	max	39	41
D28	n	38	41
	m	16.3	14.5
	sd	8.3	8.2
	min	3	2
	max	32	35
D42	n	38	41
	m	15.1	12.9
	sd	9.6	7.3
	min	0	0
	max	40	34
D56	n	38	41
	m	14.3	11.0
	sd	10.1	6.9
	min	0	0
	max	40	34

The repeated measure analysis of variance revealed a treatment group effect in favor of Deroxat® ($p = 0.004$). The decrease in the MADRS was greater over time in the Deroxat® group than in the Anafranil® group.

These results confirm the ITT analysis.

11.7. Efficacy Conclusions

All p values for efficacy are given in the following table:

p Value				
	ITT Population N = 121	PP Population N = 79	Bracket I N = 60	Bracket II N = 61
Primary Criteria No. of Complete Responders Chi 2	0.06	0.01 D > A Bracket 1: 0.19 Bracket 2: 0.04	0.71	0.002
Logistic Analysis	0.026 D > A	0.018 D > A	0.94	0.001 D > A
Odds ratio 95% CI	2.42 1.11 – 5.26	3.67 1.25 – 10.82	0.96 0.33 – 2.84	10.55 2.58 – 43.21
MADRS ANOVA	0.003 D > A	0.004 D > A	-	-
D56 CGI Global Improvement	0.71		0.08	0.46
D56 Severity	0.39	0.48	0.38	0.05
GAF ANOVA	0.57			
Early Failures	0.27			
Non-responders	0.19			

Although the population was smaller, the results of the per protocol analysis not only confirmed the results of the ITT analysis in the logistic analysis and ANOVA analysis of the MADRS, but the significance level is much higher. This increase in significance level makes the primary criterion results significant ($p = 0.06$ for the ITT population, $p = 0.01$ for the per protocol population).

All of these results are consistent and confirm the superiority of Deroxat® over Anafranil®. The fact that the per protocol population results are better even though the power is lower appears to be because 17 of the 42 patients who experienced major deviations were in the suicide center.

However, the center 7 results never allowed differentiating between the 2 treatment groups. Patients did not respond as well to either treatment. No statistically significant difference between the 2 treatment groups was demonstrated in the analysis by stratification based on age.

One out of 2 children was a complete responder (57% in the Anafranil® group versus 52.9% in the Deroxat® group.), with a much greater difference in Bracket II (40.6% in the Anafranil® group versus 79.3% in the Deroxat® group).

The Bracket II results agree completely with the work by xxxxxxxxxxxxxx, who observed complete remission and improvement of residual symptoms in 75% of adolescents receiving paroxetine, and with the work by xxxxxx on tricyclics.

The results reported by xxxxxxx concerning an SRI's effect on the CGI, where 56% of children and adolescents had improved, are once again comparable to the results from this study.

12 SAFETY EVALUATION

The safety population corresponded to the ITT population. The 4 patients from center 36 (not analyzed) experienced AEs and SAEs that were not taken into consideration in the analysis. These are given as narrative summaries.

The analyzed data are presented for the population and by age bracket for the primary evaluation up to D56.
We would like to emphasize that the wording of intercurrent events was different for each investigator: some were described as symptoms while others were described as a syndrome or diagnosis.

26 patients continued treatment beyond D56, and 8 remained in the study until the end, D168; the study of tolerance in the study patients past D56 is discussed in a separate paragraph.

12.1 Emergent Intercurrent Events

97 patients, or 80.2% of the population, presented at least one intercurrent event: 50, or 86.2%, in the Anafranil® group, and 47, or 74.6%, in the Deroxat® group.
There was no statistically significant difference between the 2 treatment groups ($p = 0.11$).

314 events were reported for these 97 patients: 178 in the Anafranil® group and 136 in the Deroxat® group.
The events are detailed below by body system.

The most numerous intercurrent events, by body system, were psychiatric disorders (47.2% in the Anafranil® group and 52.8% in the Deroxat® group) and central nervous system disorders (70.4% in the Anafranil® group and 29.6% in the Deroxat® group). These events and their incidence agree with the known characteristics of the two study treatments.

Table 37 Number of Intercurrent Events by Body System

	GROUP				
	A		B		total
	N	%	N	%	N
Body system					
			2	100.00	2
AUTONOMIC NERVOUS SYSTEM DISORDERS	2	50.00	2	50.00	4
BODY AS A WHOLE - GENERAL DISORDERS	13	43.33	17	56.67	30
CENTRAL AND PERIPHERAL NERVOUS SYST. DISORDERS	57	70.37	24	29.63	81
GASTRO-INTESTINAL SYSTEM DISORDERS	38	71.70	15	28.30	53
LIVER AND BILIARY SYSTEM DISORDERS	1	50.00	1	50.00	2
MUSCULO-SKELETAL SYSTEM, DISORDERS	2	40.00	3	60.00	5
PLATELET, BLEEDING AND CLOTTING DISORDERS			1	100.00	1
PSYCHIATRIC DISORDERS	50	47.17	56	52.83	106
REPRODUCTIVE DISORDERS, FEMALE	1	50.00	1	50.00	2
RESISTANCE MECHANISM DISORDERS			1	100.00	1
RESPIRATORY SYSTEM DISORDERS	7	63.64	4	36.36	11
SKIN AND APPENDAGES DISORDERS	6	75.00	2	25.00	8
URINARY SYSTEM DISORDERS			3	100.00	3
VASCULAR (EXTRACARDIAC), DISORDERS			1	100.00	1
VISION DISORDERS	1	50.00	1	50.00	2
WHITE CELL AND RES DISORDERS			2	100.00	2
total	178	56.69	136	43.31	314

The distribution of patients presenting at least one intercurrent events in the “centers excluding center 7” group and in center 7 is as follows:

Table 38 Distribution of Number of Patients with at least 1 IE, by Center Group

	Anafranil®	**Deroxat®**
All centers except center 7	37, or 84.1%	36, or 73.5%
Center 7 (suicide center)	13, or 92.9%	11, or 78.6%

The percentage of patients who presented at least one event was larger in the suicide center, with a higher increase in the Anafranil® group than in the Deroxat® group.

70 patients presented at least one intercurrent event between D1 and D21, and 67 between D1 and D56.

Table 39 Number of Patients with at least 1 IE, from D1 to D21 and D21 to D56

Patients with at least 1 IE	**Anafranil®**	**Deroxat®**	**p Value**
D1 – D21	37, or 63.8%	33, or 52.4%	0.204
D21 – D56	35, or 60.3%	32, or 50.8%	0.204

There was no difference over time for either Anafranil® or Deroxat®.

12.2. Serious Intercurrent Events

32 serious events were recorded. The definition of a serious event was:

- death,
- effect on life expectancy,
- temporary or permanent incapacity,
- hospitalization or prolongation of hospitalization,
- congenital abnormality,
- cancer,
- overdose (accidental or intentional).

These 32 events were reported by 9 patients in the Anafranil® group, or 15.5%, versus 13 patients in the Deroxat® group, or 20.6%. There was no statistically significant difference (p = 0.47) between the 2 treatment groups.

The events were distributed as follows: 11 in the Anafranil® group and 21 in the Deroxat® group.

Details of the serious events are given in the following table:

Table 40 List of Serious Intercurrent Events

Anafranil® group

Center	Patient no.	Bracket	Event	Time to Onset* /D1 (in days)	Duration* (in days)	Exclude patient
7	97	I	INTENTIONAL INHALATION OF VENTOLINE	59	2	no
7	147	I	INTENTIONAL DRUG INGESTION = LYSANXIA	26	1	no
7	527	II	SUICIDE ATTEMPT BY TAKING BIACTOL	12	1	yes
7	549	II	PANIC ATTACK	13	1	yes
7	549	II	SUICIDE ATTEMPT BY CUTTING	13	1	yes
7	608	II	SUICIDE ATTEMPT BY INTENTIONAL DRUG INGESTION	32	1	yes
7	669	II	SUICIDE ATTEMPTS	25	1	yes
9	29	I	MOOD SWINGS	13	13	yes
15	49	I	AGRESSIVENESS	20	8	no
15	49	I	IRRITABILITY	20	8	no
20	577	II	INTENTIONAL OVERDOSE	55	2	yes
Deroxat® group						
7	24	I	INTENTIONAL OVERDOSE	54	1	no
7	99	I	INTENTIONAL DRUG OVERDOSE	53	1	no
7	99	I	INCREASED ANXIETY	41	.	yes
7	144	I	PROZAC STUDY DRUG + ALCOHOL OVERDOSE	6	2	yes
7	144	I	MAJOR ANXIETY	9	1	yes
7	649	II	INTENTIONAL OVERDOSE	17	1	yes
11	39	I	PSYCHOMOTOR DISINHIBITION	15	1	yes
11	543	I	THREATENS TO HARM SELF, REQUIRING	23	4	yes
11	543	I	AGGRAVATION OF DEPRESSIVE STATE	23	68	yes
14	46	I	SUICIDE ATTEMPT (OVERDOSE)	10	3	yes
14	668	I	RE-HOSPITALIZED AT FAMILY REQUEST FEARING AGGRAVAT	35	16	no
21	73	I	DENTAL CELLULITIS	25	.	no
21	73	I	PARACETAMOL OVERDOSE	24	.	yes
27	663	II	SCHIZOPHRENIC SYNDROME	22	47	no
29	115	I	MANIC EPISODE	18	.	yes
29	115	I	DELIRIUM	18	.	yes
29	116	II	XANAX OVERDOSE	3	2	no
29	116	II	BEHAVIORAL PROBLEMS	17		yes
29	116	II	INHIBITION	17	.	yes
38	162	I	BEHAVIORAL PROBLEMS AND DRUG TAKING	39	3	yes
38	162	I	BORDERLINE PSYCHOTIC DISINHIBITION RELATED TO	41	16	yes

7 suicide attempts were made in the Anafranil® group, and 8 in the Deroxat® group. A manic mood swing was recorded in the Anafranil® group; two cases of disinhibition, one manic episode and behavioral problems were recorded in the Deroxat® group.

12.3. Events Deemed Severe by the Investigator

The investigator qualified 67 events as severe, 31 in the Anafranil® group and 36 in the Deroxat® group.

These 67 events were reported in 21 Anafranil® group patients and 20 Deroxat® group patients. There was no statistically significant difference ($p = 0.61$) between the 2 treatment groups.

Details of these events are given in the following tables:

Table 41 List of Severe AEs

Anafranil® Group

Center	Patient no.	Bracket	Event	Time to Onset* /D1 (in days)	Duration* (in days)	Serious AE	Exclude patient
1	501	II	FEELINGS OF VERTIGO	1	.	no	no
1	501	II	TREMBLING	1	.	no	no
4	13	I	NAUSEA	2	2	no	yes
7	17	I	ACUTE SOMATIC ANXIETY	7	1	no	no
7	97	I	INTENTIONAL INHALATION OF VENTOLINE	59	2	yes	no
7	147	I	INTENTIONAL DRUG TAKING = LYSANXIA	26	1	yes	no
7	526	II	CONSTIPATION	28	14	no	no
7	526	II	WORSENED CONSTIPATION	41	.	no	no
7	527	II	ANXIETY RELAPSE	9	.	no	no
7	549	II	PANIC ATTACK	13	1	yes	yes
7	608	II	FLU SYNDROME	16	5	no	no
7	650	II	NAUSEA	0	7	no	yes
7	650	II	TREMBLING OF UPPER LIMBS	0	7	no	yes
7	650	II	NOCTURNAL INSOMNIA	0	7	no	yes
7	650	II	HEADACHE	0	7	no	yes
7	650	II	DRY MOUTH	0	7	no	yes
7	650	II	NIGHT SWEATS	0	7	no	yes
8	26	I	DIFFICULTY FALLING ASLEEP	7	3	no	no
8	529	II	ACUTE NOCTURNAL ANXIETY ATTACKS	31	1	no	no
8	530	II	TOOTHACHE	28	1	no	no
9	533	II	NAUSEA	1	.	no	yes
11	544	II	ASTHMA ATTACK	26	.	no	no
11	630	II	HEAD COLD	39	3	no	no
14	45	I	PELVIC PAIN	51	1	no	no
14	48	I	VIOLENT HEADACHE	0	.	no	no
14	48	I	FEELINGS OF VERTIGO AND HYPOTENSION	2	.	no	no
29	113	I	INCREASED INSOMNIA	1	56	no	no
29	113	I	RUSH EFFECT PSYCHOMOTOR EXCITATION	1	1	no	no
29	131	I	HYPERSOMNIA	11	30	no	no
32	621	II	JAW TREMOR	1	2	no	yes
32	621	II	FEELINGS OF VERTIGO	1	2	no	yes

Deroxat® Group

Center	Patient no.	Bracket	Event	Time to Onset* /D1 (in days)	Duration* (in days)	Serious AE	Exclude patient
1	638	II	LIGHT-HEADEDNESS	2	3	no	no
1	638	II	DRY MOUTH	2	3	no	no
7	99	I	INCREASED ANXIETY	41	.	yes	yes
7	99	I	INCREASED DIFFICULTY FALLING ASLEEP	41	.	no	no
7	144	I	PROZAC STUDY DRUG + ALCOHOL OVERDOSE	6	2	yes	yes
7	144	I	MAJOR ANXIETY	9	1	yes	yes
7	605	II	MAJOR DAYTIME SOMNOLENCE THAT AFFECTS	1	8	no	no
7	649	II	ANXIETY	3	.	no	no
7	649	II	INTENTIONAL OVERDOSE	17	1	yes	yes
7	670	II	AGITATION	1	1	no	no
8	25	I	ANXIETY ATTACK	3	1	no	no
8	25	I	ANXIETY ATTACK WITH FEELING OF RELATIVE	4	1	no	no
8	25	I	ANXIETY ATTACK WITH AGITATION	5	1	no	no
8	25	I	ANXIETY ATTACK WITH DESTRUCTIVE AGITATION	7	1	no	yes
11	39	I	PSYCHOMOTOR DISINHIBITION	15	1	yes	yes
11	542	I	DIFFICULTY FALLING ASLEEP	2	7	no	no
11	543	I	INTESTINAL GAS	2	9	no	no
11	543	I	THREATENS TO HARM SELF, REQUIRING	23	4	yes	yes
11	543	I	AGGRAVATION OF DEPRESSIVE STATE	23	68	yes	yes
14	46	I	SUICIDE ATTEMPT (OVERDOSE)	10	3	yes	yes
14	47	I	DYSURIA	4	1	no	no
14	47	I	HARMS SELF	18	5	no	no
20	69	I	ORTHOSTATIC HYPOTENTION	2	6	no	no
21	73	I	DENTAL CELLULITIS	25	.	yes	no
27	610	II	SEDATION	1	1	no	yes
27	610	II	ORTHOSTATIC HYPOTENTION	1	1	no	yes
27	663	II	CATATONIC SYNDROME	16		no	yes
27	663	II	SCHIZOPHRENIC SYNDROME	22	47	yes	no
29	115	I	MANIC EPISODE	18	.	yes	yes
29	115	I	DELIRIUM	18	.	yes	yes
29	116	II	BEHAVIORAL PROBLEMS	17		yes	yes
29	116	II	INHIBITION	17	.	yes	yes
32	622	II	ANXIETY AND REPRESSIVE RELAPSE	16	7	no	no
38	162	I	SLEEPING DISORDER - DIFFICULTY FALLING ASLEEP	22	.	no	no
38	162	I	BEHAVIORAL PROBLEMS WITH DRUG TAKING	39	3	yes	yes
38	162	I	BORDERLINE PSYCHOTIC DISINHIBITION RELATED TO	41	16	yes	yes

In the Anafranil® group in particular we found the side effects (dry mouth, constipation, nausea, trembling, etc.) that are characteristic of this therapeutic class.

12.4 Adverse Events in Relation to the Treatment

The investigator considered 160 of the 314 intercurrent events to be possibly or probably related to the treatment, so these were qualified as adverse events.

These 160 adverse events were distributed as follows:

- 101 adverse events in 40 Anafranil® group patients (69%),
- 59 adverse events in 31 Deroxat® group patients (49.2%).

There was a statistically significant difference ($p = 0.03$) between the 2 treatment groups in favor of Deroxat®.

Of the adverse events considered severe by the investigators and related to the treatment, 18 occurred in the Anafranil® group in 9 patients, and 23 occurred in 15 patients in the Deroxat® group. There was no statistically significant difference ($p = 0.25$) between the 2 treatment groups.

12.5 Intercurrent Events and Withdrawals from the Study

13 patients in the Anafranil® group withdrew from the study early due to intercurrent events (a total of 28 IEs). In the Deroxat® group, 14 patients experienced a total of 20 events which caused them to withdraw from the study.
There was no difference between the 2 treatment groups ($p = 0.99$).

The list of the events leading to withdrawal from the study are given in the following table:

Table 42 List of AEs that Led to Discontinuation of Treatment

Anafranil® Group

Center	Patient no.	Bracket	Event	Time to Onset* /D1 (in days)	Duration* (in days)	Serious AE
	505	II	FEELS UNWELL UPON RISING IN THE MORNING	2	.	no
2	505	II	ACCOMMODATION PROBLEMS	2	.	no
2	505	II	FEELINGS OF DESPAIR	2	.	no
4	13	I	NAUSEA	2	2	no
4	13	I	TREMBLING	2	1	no
4	13	I	SKIN PALLOR	2	1	no
4	13	I	HEADACHE	2	2	no
4	13	I	GASTRALGIA	2	.	no
7	527	II	SUICIDE ATTEMPT BY TAKING BIACTOL	12	1	yes
7	549	II	PANIC ATTACK	13	1	yes
7	549	II	SUICIDE ATTEMPT BY CUTTING	13	1	yes
7	608	II	SUICIDE ATTEMPT BY INTENTIONAL DRUG INGESTION	32	1	yes
7	650	II	NAUSEA	0	7	no
7	650	II	TREMBLING OF UPPER LIMBS	0	7	no
7	650	II	NOCTURNAL INSOMNIA	0	7	no
7	650	II	HEADACHE	0	7	no
7	650	II	DRY MOUTH	0	7	no
7	650	II	NIGHT SWEATS	0	7	no
7	669	II	SUICIDE ATTEMPT	25	1	yes
8	530	II	IRRITABILITY	29	11	no
8	530	II	SWEATING	28	12	no
9	29	I	MOOD SWINGS	13	13	yes
9	533	II	NAUSEA	1	.	no
9	533	II	HYPOTENSION	2	.	no
15	644	II	DRY MOUTH	28	5	no
20	577	II	INTENTIONAL OVERDOSE	55	2	yes
32	621	II	TREMBLING OF THE JAW	1	2	no
32	621	II	FEELINGS OF VERTIGO	1	2	no

Deroxat® Group

Center	Patient no.	Bracket	Event	Time to Onset* /D1 (in days)	Duration* (in days)	Serious AE
7	99	I	INCREASED ANXIETY	41	.	yes
7	144	I	PROZAC STUDY DRUG + ALCOHOL OVERDOSE	6	2	yes
7	144	I	MAJOR ANXIETY	9	1	yes
7	525	II	MANIC SWINGS	7	.	no
7	649	II	INTENTIONAL DRUG OVERDOSE	17	1	yes
8	25	I	ANXIETY ATTACK WITH DESTRUCTIVE AGITATION	7	1	no
11	39	I	PSYCHOMOTOR DISINHIBITION	15	1	yes
11	543	I	THREATENS TO HARM SELF, REQUIRING	23	4	yes
11	543	I	AGGRAVATION OF DEPRESSIVE STATE	23	68	yes
14	46	I	SUICIDE ATTEMPT (OVERDOSE)	10	3	yes
21	73	I	PARACETAMOL OVERDOSE	24	.	yes
27	610	II	SEDATION	1	1	no
27	610	II	ORTHOSTATIC HYPOTENSION	1	1	no
27	663	II	CATATONIC SYNDROME	16	.	no
29	115	I	MANIC EPISODE	18	.	yes
29	115	I	DELIRIUM	18	.	yes
29	116	II	BEHAVIORAL PROBLEMS	17	.	yes
29	116	II	INHIBITION	17	.	yes
38	162	I	BEHAVIORAL PROBLEMS AND DRUG TAKING	39	16	yes
38	162	I	BORDERLINE PSYCHOTIC DISINHIBITION RELATED TO	41	16	yes

12.6. Safety Evaluation by Age Bracket

All tolerance results by age bracket are given in the following table:

Table 43 Patient and Event Distribution for the Different Types of AEs, by Age Bracket

Bracket I	**Anafranil® n=26**	**Deroxat® n=34**	**p Value**
Patients with at least 1 AE	96.2% (n=25) = 84 AE	79.4% (n=27) = 86 AE	0.12
Patients with at least 1 SAE	15.4% (n=4) =5 SAE	29.4% (n=10) =16 SAE	0.20
Patients with at least 1 severe AE	34.6% (n=9) or 11 AE	35.3% (n=12) or 23 AE	0.96
Patients with at least 1 AE related to treatment	69.2% (n=18) = 43 AE	55.9% (n=19) = 36 AE	0.29
Patients with at least 1 severe AE related to treatment	15.4% (n=4) = 5 AE	29.4% (n=10) = 15 AE	0.20
Patients with AE and early withdrawal	7.7% (n=2) = 6 AE	26.5% (n=9) = 13 AE	0.09
Bracket II	**Anafranil® n=32**	**Deroxat® n=29**	**p Value**
Patients with at least 1 AE	78.1% (n=25) = 94 AE	69.0% (n=20) = 50 AE	0.42
Patients with at least 1 SAE	15.6% (n=5) =6 SAE	10.3% (n=3) =5 SAE	0.71
Patients with at least 1 severe AE	37.5% (n=12) or 20 AE	27.6% (n=8) or 13 AE	0.41
Patients with at least 1 AE related to treatment	68.8% (n=22) = 58 AE	41.4% (n=12) = 23 AE	**0.03**
Patients with at least 1 severe AE related to treatment	15.6% (n=5) = 13 AE	17.2% (n=5) = 8 AE	1
Patients with AE and early withdrawal	34.4% (n=11) = 22 AE	17.2% (n=5) = 7 AE	0.13

The evidence shows that nearly all patients in Bracket I experienced at least one AE in the Anafranil® group. Events were considered serious more often in the Deroxat® group; 9 patients in the Deroxat® group withdrew early while 2 patients in the Anafranil® group withdrew early ($p = 0.09$), although these results are not statistically significant. This safety profile, specific to the younger children, may be related to the sex ratio, which, as noted earlier, was different for Bracket I (20 boys in the Deroxat® group and 8 in the Anafranil® group).

There was a statistically significant difference in favor of Deroxat® in Bracket II: 22 patients in the Anafranil® group experienced at least one treatment-related AE versus 12 patients in the Deroxat® group. No significant differences were observed for other parameters.

12.7 Safety for the Period from D56 to D168

Recall that 26 patients continued treatment beyond D56, and 8 remained in the study until the end, or D168.

14 patients (3 in the Anafranil® group and 11 in the Deroxat® group) experienced at least one intercurrent event after D56.
25 events were reported: 7 in the Anafranil® group and 18 in the Deroxat® group.

The 2 serious events for this period, in the Deroxat® group, are given below:

Table 44: List of Serious Events in the Period from D56 to D168

Group	*Center*	*No.*	*Verbatim Report*	*Time to Onset/D1 (in days)*	*Relation*	*Duration (in days)*	*Exclude patient*
B	*11*	*37*	*REACTIONAL AGITATION*	*147*	*excluded*	*1*	*no*
B	*15*	*642*	*PREGNANCY*	*127*	*excluded*		*yes*

Of the 25 events in this period:
- 4 occurring in patients from the Deroxat® group were considered severe, i.e.:

Group	*Center*	*Patient No.*	*Verbatim Report*	*Duration (in days)*	*Time to Onset*/D1(in days)*
B	*11*	*542*	*RHINOPHARYNGITIS*	*9*	*72*
	11	*542*	*CRYING SPELLS*	*4*	*120*
	22	*78*	*DIFFICULTY FALLING ASLEEP*	*3*	*75*
	37	*165*	*HYPNAGOGIC HALLUCINATIONS*	*2*	*91*

- 6 events were (2 in the Anafranil® group and 4 in the Deroxat® group) were attributable to the study product, i.e.:

group = A

center	Patient no.	AE	Intensity	Duration* (in days)	Time to Onset*/D1 (in days)
11	38	MEMORY LAPSES	1	.	102
11	38	NERVOUSNESS	2	.	120

group = B

center	Patient no.	AE	Intensity	Duration* (in days)	Time to Onset*/D1 (in days)
22	78	DIFFICULTY FALLING ASLEEP	3	3	75
32	622	ANXIETY DEPRESSION RELAPSE	2	.	99
32	637	WEIGHT GAIN 4KG IN 1	1	29	127
37	165	HYPNAGOGIC HALLUCINATIONS	3	2	91

- 2 events in the Deroxat® group led to discontinued treatment (one pregnancy and one 4-kg weight gain):

center	Patient no.	AE	Intensity	Duration* (in days)	Time to Onset/D1 (in days)
15	642	PREGNANCY	.	.	127
32	637	WEIGHT GAIN 4KG IN 1	1	29	127

13 DISCUSSION AND OVERALL CONCLUSION

For the primary criterion, the ITT analysis demonstrated that the efficacy of Deroxat® is at least equivalent to that of Anafranil®: The number of complete responders was 65.1% in the Deroxat® group versus 48.3% in the Anafranil® group ($p = 0.06$). The per protocol analysis allowed us to reach significance ($p = 0.01$). This observed response level agrees with that reported in the literature with another SRI (10).

The analysis of secondary criteria supported these results, especially in terms of a reduction in MADRS score ($p = 0.026$) and the evolution of the MADRS score over time ($p = 0.03$), in which Deroxat® was shown to be superior to Anafranil®.
In addition, the patients' status improved in their psychological, social, and occupational functioning, as shown by the analysis of the GAF. The percentages of global improvement (assessed using the CGI) were interchangeable in both groups at D21 ($p = 0.73$) and at D56 ($p = 0.71$).

(Analysis by bracket showed a very similar efficacy ($p = 0.71$) for both treatments in the youngest patients in Bracket I (12 – 16 years old). In Bracket II (patients aged 16 to 20 years), the number of responders in the Deroxat® group (79.3%) was significantly higher ($p = 0.002$) than that found in the Anafranil® treatment group (40.6%).)

Note that the Anafranil® dose used for the first 3 weeks of treatment may appear low for older adolescents. Investigators chose this dose because young subjects were participating in the study. However, note that investigators rarely increased the Anafranil® dosage when they were allowed the possibility at D21: only 4 doses were doubled in bracket II for 22 adolescents.

The tolerance profile for Deroxat® and Anafranil® in patients aged 12 to 20 years was similar to that reported in adults, and events and their incidence agreed with the known characteristics of the products. Intercurrent events related to Deroxat® were not as numerous as those related to Anafranil® in Bracket II ($p = 0.03$), except for events considered severe by the investigator; these were equally distributed between the two groups.

This study therefore demonstrated that the efficacy of Deroxat® is at least equivalent to that of Anafranil® for treating major unipolar depression in young subjects (12 to 20 years old), and that the tolerance profile for Deroxat® matched the known characteristics of the product in the treatment of major depressive episodes in adults.

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

15. REFERENCE LIST

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On May 6, 2004, before me, Kerri Kristen Palitang, Notary Public, personally appeared Gabriel A. Rodino, who identified himself to me by presenting his driver's license, and is the person whose name is subscribed to the within instrument, and he acknowledged to me that he executed the same in his authorized capacity, and that by his signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

Kerri Kristen Palitang
Signature of Notary

KERRI KRISTEN PALITANG
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WITNESS my hand and official seal.

Kerri Kristen Palitang
Signature of Notary

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