Janssen Research & Development

Clinical Study Report Synopsis
[C-98-012-05; Phase 3]

JNJ-629330-AAC (Methylphenidate HCl)

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- Information (including individual data listings, where applicable) has been removed or redacted to protect the privacy of patients, study subjects, and all named persons associated with the study. Names of companies other than Janssen Research & Development or Johnson & Johnson affiliates have been redacted, unless a contractual agreement is in place with those companies to disclose their names.
- Information has been removed or redacted to protect commercially confidential information.
- Aggregate data have been included, with any direct reference to an individual patient or study subject excluded.
- To disclose as much scientifically useful data as possible, no information other than that outlined above has been removed or redacted.

SYNOPSIS (Page 1 of 6)

Company: ALZA Corporation **Investigational product:** OROS® (methylphenidate HCl) **Active ingredient:** methylphenidate hydrochloride		
Title: Long-term Safety and Effectiveness of OROS® (methylphenidate HCl) in Children with ADHD (Part I and Part II)	**Trial No.:** C-98-012-05 **Clinical phase:** III	
Investigators: Multicenter	**Country:** USA	

Report date: F ebruary 2003	
Trial period: Star t: June 1998 End: December 2000	**No. of investigators:** 14 **No. of patients:** Part I: 436 enrolled/289 completed Part II: 278 enrolled/229completed
Indication: Treatment of children with attention deficit hyperactivity disorder (ADHD)	

Objectives:

Part I:
1) To evaluate the long-term safety of OROS® (methylphenidate HCl) in children with attention deficit hyperactivity disorder.
2) To evaluate the effectiveness and use of OROS® (methylphenidate HCl).

Part II:
1) To evaluate the long-term safety of OROS® (methylphenidate HCl) in children with attention deficit hyperactivity disorder who had taken OROS® (methylphenidate HCl) for one year in Part I of the study.
2) To evaluate the effectiveness and clinical use of OROS® (methylphenidate HCl).

Trial design: This was a multicenter, open-label, non-randomized study to evaluate the long-term safety of OROS® (methylphenidate HCl) in up to 486 children 6 to 13 years of age with ADHD

Patient selection:

Inclusion criteria:

Part I: For participation in Part I of the study, patients:

1. Who successfully completed the previous ALZA study (C-97-025, C-97-033 [and then successfully completed C-98-011], C-98-003, or C-98-005) without significant drug-related adverse events. Patients who discontinued C-98-005 early because of lack of efficacy that could not be tolerated were allowed to enroll in this study with sponsor approval.
2. Whose primary care physician agreed that it was appropriate to participate in the study.
3. Who agreed to take only the OROS® (methylphenidate HCl) supplied and no other methylphenidate dosage form or other medications for the treatment of ADHD during the study.
4. Who were able to comply with the study visit schedule and whose parent(s) and teachers were willing and able to complete the protocol-specified assessments.
5. Who were able to understand that they could withdraw from the study at any time.
6. Who signed an assent form and whose parent/caregiver signed a consent form.
7. Who had normal urinalysis, hematological and blood chemistry values, or, if the values were outside the normal range, they were determined not clinically significant by the investigator, either at the start of the previous ALZA study, or at screening for this study.

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Patient selection (continued):

Inclusion Criteria (continued)

Part II: For participation in Part II, patients:

1. Who continued to meet all of the eligibility criteria for Part I of the study except that teachers were no longer required to participate as detailed in Inclusion Criteria 4 in Part I above.
2. Who successfully completed Part I of this study.
3. Who were 7 to 15 years of age.

Exclusion Criteria:

Part I: The following patients were ineligible for participation in Part I:

1. Who had clinically significant gastrointestinal problems, including narrowing (pathologic or iatrogenic) of the gastrointestinal tract.
2. Who had any coexisting medical condition or who were taking any concomitant medication that was likely to interfere with safe administration of methylphenidate, in the investigator's opinion.
3. Who had a known hypersensitivity to methylphenidate.
4. Who had a history of hypertension or who had a blood pressure (systolic or diastolic) equal to or greater than the 95th percentile for age, gender, and height, as outlined in Appendix 2 of the protocol (Appendix 12.1.1 of this report), determined at screening for the previous ALZA study. If more than 4 weeks had elapsed since completion of the previous ALZA study, blood pressure measurements were to be repeated at screening for this study.
5. Females who had reached menarche.

Part II: Patients who met any of the Exclusion Criteria in Part I above were ineligible to participate in Part II, except that females who reached menarche (after protocol amendment 5 was enacted) were allowed to participate in Part II at the discretion of the clinical investigator and with the prior approval of the ALZA Medical Monitor.

Treatments: OROS® (methylphenidate HCl) 18 milligram (mg) systems (capsule-shaped tablets). During Part I of the study patients received doses of 18 mg, 36 mg, or 54 mg once a day, as determined by the results from their participation in earlier ALZA studies C-97-025, C-97-033, C-98-003, C-98-005, or C-98-007. Patients who participated in Part II of the study continued to receive a daily dose determined from the dosing at the end of Part I. Doses could have been titrated up or down to a maximum of 54 mg/day, as considered appropriate by the medical personnel at the study site. The control numbers for lots used were 9800064 (Code number 0007974), 9800299 (Code number 0008178), 9800306 (Code number 0008178), and 9804932 (Code number 0008602).

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Assessments	**Part I**						**Part II**			
	Study Screening	Study Visit 1 Part I	Monthly	Every 3 Months	Every 6 Months	End of Part I Study Visit[g]	Study Visit 1 Part II	Monthly[f]	Every 3 Months	Study Termination
Informed Consent		X					X			
Physical Examination	X[b]					X				X
Height and Weight	X	X				X[a]			X	X[e]
Blood pressure and pulse	X	X	X		X			X		X
Dispense study drug		X X					X	X X		
Compliance		X			X			X	X	X
Concomitant medications		X	X		X			X		X
Determine menarche status							X	X	X X	
Adverse events		X			X			X		X
Appetite, sleep, tics (parent rating)		X	X		X					
Blood and urine sample	X[c]				X	X				X
IOWA Conners			P,T[d]							
Peer Interaction items			T							
Parent Satisfaction Questionnaire			P (1 month only)	P		P			X	X
Global Assessment				P,T[d]	P		I		P,I	P,I

[a] For children terminated early because of growth problems, post-treatment assessments were done monthly for three months.

[b] For patients who participated in C-97-025 and C-97-033, and completed those studies more than four weeks prior to enrolling in this study, a physical examination was done at screening. A physical examination was not required for patients who completed C-98-003 or C-98-005 within four weeks of enrolling in this study.

[c] For patients who participated in C-97-025 and C-97-033, blood and urine samples were taken at screening for this study. Blood and urine samples were not required for patients who completed C-98-003 or C-98-005 within four weeks of enrolling in this study.

[d] P = parent/caregiver; T = community school teacher; I = investigator; The Community school teacher global assessment was also done at the end of the school year.

[e] For children who terminated the study early because of growth problems, post-treatment assessments were repeated three months following termination.

[f] Visit was with parent/caregiver only, unless an assessment for a medication dose adjustment was needed, in which case the child accompanied the parent/caregiver.

[g] For patients who did not continue into Part II of the study, this Study Visit represented the final study visit (Study Termination).

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MEASUREMENTS

Efficacy

Standardized measurements of attention, behavior, and hyperactivity were conducted and included:

1. Inattention Overactivity with Aggression (IOWA) Conners Rating Scale (Inattention/Overactivity [I/O] and Oppositional/Defiance [O/D] subscales) and Peer Interaction assessment by the community school teacher every month during the school year during Part I of the study.
2. IOWA Conners Rating Scale (I/O and O/D subscales) assessment by the parent/caregiver every month during Part I.
3. Global evaluation of effectiveness of OROS® (methylphenidate HCl) therapy for the treatment of ADHD by the parent/caregiver and the teacher every 3 months during Part I, and every three months by the parent/caregiver and by the investigator during Part II of the study.
4. Completion of the Parent Satisfaction Questionnaire by the parent/caregiver at 1, 6, and 12 months during Part I, and at 3-month intervals during Part II of the study.

Usage of OROS® (methylphenidate HCl) was evaluated by following dose changes during Parts I and II of the study over an approximately 27-month period.

Safety

The following safety measures were evaluated at baseline, at intervals during the study, and at study completion.

1. Pulse; blood pressure; height; weight; and sleep quality, appetite, and tics (parent rating) were evaluated monthly during Part I of the study. During Part II, pulse, blood pressure, height, and weight were evaluated every 3 months.
2. Hematology, blood chemistries, and urinalysis were measured at baseline, at 6 and 12 months, at study completion, and for those patients continuing in Part II at the end of Part I study visit.
3. A physical examination was performed at baseline, at study completion, and for those patients continuing in Part II, at the end of Part I study visit.
4. Spontaneous reports of adverse events were recorded throughout the study.

Statistics

Descriptive statistics were used to summarize the information collected in this study.

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RESULTS

DEMOGRAPHICS: Baseline Characteristics and Subject Disposition

Number of patients[a] (M/F)	338/69
Age: mean (min-max), y	9.2 (6-13)
Drop-outs (Part I) - reason	31 (7.6%): Lack of efficacy 24 (5.9%): Adverse event or intercurrent illness 15 (3.7%): Lost to follow-up 13 (3.2%): Other 11 (2.7%): Noncompliance 11 (2.7%): Personal reason 6 (1.5%): Female patient reached menarche[b] 3 (0.7%): Adverse event requiring dose reduction below 18 mg 3 (0.7%): Protocol violation 1 (0.2%): Blood pressure
Drop-outs (Part II) - reason	14 (5.0%): Lost to follow-up 11 (4.0%): Noncompliance 6 (2.2%): Personal reason 5 (1.8%): Lack of efficacy 3 (1.1%): Adverse event or intercurrent illness 3 (1.1%): Female patient reached menarche[b] 3 (1.1%): Protocol violation 3 (1.1%): Other 1 (0.4%): Coexisting medical condition

[a] All patients who were enrolled and treated with study drug, except for those enrolled at Site [redacted]

[b] During Part I, females who had reached menarche was an exclusion criteria, whereas during Part II, after Protocol Amendment 5 was enacted, females who reached menarche were allowed to participate in Part II at the discretion of the clinical investigator and with the prior approval of the ALZA Medical Monitor.

Efficacy: The results based on data for the 407 patients enrolled and treated in Part I of this study [efficacy data of Site [redacted] patients ([redacted] were excluded due to unreliable data] and the 277 patients enrolled and treated in Part II of this study support the following conclusions:

- Efficacy was demonstrated by large observed decreases in IOWA Conners Rating subscales for I/O and O/D by community school teachers and by parents or caregivers through one year for patients previously on placebo in a prior study.
- Efficacy of OROS® (methylphenidate HCl) for treating ADHD was maintained through one year during follow-up treatment months, regardless of prior treatment of patients, as evidenced by comparable mean values (to the last assessment in a previous study) of IOWA Conners Inattention/Overactivity (I/O) and Oppositional/Defiance (O/D) subscale ratings by community school teachers and parent/caregivers.
- Peer interaction assessed by community school teachers was maintained through one year.
- Global evaluations at 6 and 12 months showed that 61.4% and 63.0%, respectively, of community school teachers, and 89.1% and 90.6%, respectively, of parents or caregivers rated the OROS® (methylphenidate HCl) treatment as good or excellent. Parent or caregiver ratings were similar during year 2 of the study, and at 27 months, 87.5% of parents or caregivers and 87.0 % of investigators rated the OROS® (methylphenidate HCl) treatment as good or excellent.
- At all parent satisfaction evaluations on study (every 6 months in year 1 and every 3 months in year 2 through Month 27), more than 93% of parents said they were extremely pleased, very pleased, or pleased with OROS® (methylphenidate HCl) for the treatment of ADHD.

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RESULTS

Safety:

- Ten patients reported a serious adverse event (SAEs), none related to study medication, and two patients reported a significant non-serious AE (tics and hallucination).
- Overall, OROS® (methylphenidate HCl) was well tolerated, and there were no new safety issues identified. The AEs most frequently reported were headache, upper respiratory tract infection, pharyngitis, insomnia, cough, accidental injury, fever, abdominal pain, and anorexia. These AEs are not unexpected, are childhood illnesses, or well-known effects of methylphenidate in children.
- The overall safety profile of OROS® (methylphenidate HCl) during treatment of up to 27 months was similar to that seen previously in children treated for shorter periods.
- Minimal increases in blood pressure and pulse were observed, as expected with stimulant treatment, and did not appear to be clinically significant.

CONCLUSIONS

Efficacy was maintained throughout follow-up visits during treatment with OROS® (methylphenidate HCl) for up to 27 months. When patients previously on placebo treatment in a prior study were switched to OROS® (methylphenidate HCl), large decreases in IOWA Conners I/O and O/D subscales at the Month 1 visit were observed, compared with the last assessment from a previous study.

Overall, OROS® (methylphenidate HCl) was well tolerated, and there were no new safety issues identified.