Candesartancilexetil Study D2451C00002-328
TABLE OF CONTENTS

Drug substance(s):	Candesartan cilexetil	**SYNOPSIS**	
Edition No.:	1		
Study code:	D2451C00002/Study 328		
Date:	25 March 2009		

A Dose-ranging, Safety and Pharmacokinetics Study of Candesartan Cilexetil in Hypertensive Pediatric Subjects 1 to Less Than 6 Years of Age: A 4-week, Multicenter, Randomized, Double-Blind Study with a 1-year Open-label, Follow-up Period

Study center(s): 18 sites in the United States/Puerto Rico and 20 in Europe enrolled and treated at least 1 subject

Publications: None at the time of writing this report.

Study dates		**Phase of development**
First subject enrolled	04 November 2004	IIIB/Pediatric Programs
Last subject completed	07 August 2008	

Objectives: The primary objective of this study was to characterize the dose response relationship of candesartan cilexetil once-daily (hereafter referred to as candesartan) in hypertensive pediatric subjects (1 to <6 years of age) by evaluation of the slope of the linear regression for the change in trough systolic blood pressure (SBP) from baseline (Day 0) to the end of the 4-week, double-blind treatment period (Day 28) as a function of dose.

The secondary objectives were to further evaluate the antihypertensive effects and the safety of candesartan by determining:

- Change from Day 0 to Day 28 for the dose response relationship of candesartan for the change in trough SBP as a function of dose for each of the 2 body weight panels, separately; for the change in trough diastolic blood pressure (DBP) as a function of dose; and for the mean change in trough SBP and DBP for candesartan for each assigned dose level.
- The mean change in urinary protein/creatinine (P/C) and albumin/creatinine (A/C) ratio for each assigned dose level from baseline to Day 28 and to the end of the 52-week, open-label treatment period.

- Safety as assessed by adverse events (AEs), drug discontinuations due to AEs, serious AEs (SAEs), physical exam findings, growth, and laboratory tests results during the 4-week, double-blind treatment period and the 52-week, open-label treatment period.

- The pharmacokinetics (PK) of candesartan

Study design: Study 328 was a multicenter, dose-ranging study of candesartan in hypertensive pediatric subjects ages 1 to <6 years. It employed a double-blind, randomized, dose-ranging design followed by a 52-week, open-label treatment experience evaluation.

Subjects underwent a screening evaluation, then a 1-week, single-blind, placebo run-in period, after which eligible subjects received ½ the dose until Day 7. If tolerated, dose was increased to full dose: subjects were allocated to receive 1 of 3 dose levels of candesartan (0.05 mg/kg, 0.2 mg/kg, or 0.4 mg/kg), liquid formulation, in a 1:1:1 ratio. The study drug concentration was adjusted to correspond to a fixed dose volume (5 ml for subjects <25 kg and 10 ml for those ≥25 kg). Subjects returned weekly during the double-blind period (Day 1 to Day 28) and periodically during the 52-week, open-label treatment period.

Target subject population and sample size: The study population included male and female subjects 1 to <6 years of age with mild to moderate hypertension defined as reproducible mean SBP and/or DBP equal to or exceeding the 95th percentile of the population blood pressure distribution adjusted for height, age and gender, and ≤20 mmHg (systolic) and 10 mmHg (diastolic) above the 95th percentile.

Investigational product and comparator(s): dosage, mode of administration, and batch numbers: Candesartan in doses of 0.05 mg/kg, 0.2 mg/kg, or 0.4 mg/kg was administered once-daily in oral suspension form (the concentration of the suspension was custom prepared for each subject).

Duration of treatment: The study included a 1-week, single-blind, placebo run-in and a 4-week, double-blind treatment period followed by a 1-year, open-label treatment period.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics: The primary efficacy outcome measure was the slope by linear regression for the change from baseline in trough SBP at double-blind Week 4 as a function of candesartan dose. Secondary measures of effect included: dose response for each weight stratum for change in trough SBP; dose response for DBP; and treatment effect of each dose relative to baseline in trough SBP and DBP, and median change in urinary protein/creatinine (P/C) ratio and albumin/creatinine (A/C) ratio. Ten subjects were also enrolled in the PK substudy. The PK parameters included the time to maximum plasma concentration (t_{max}), maximum plasma candesartan concentration (C_{max}), terminal elimination half-life ($t_{1/2}$), and AUC.

Safety: AEs served as the primary safety measure.

Statistical methods: The primary efficacy analysis was based on the intent-to-treat (ITT) population and tested the null hypothesis that the slope=0 in a linear regression model with change in trough SBP as the dependent variable and dose pooled across weight panels as the independent variable. For subjects missing a double-blind, Week 4 blood pressure determination, a value was imputed by carrying the last observation forward (LOCF).

Subject population: Although the dose-specific groups were not large (0.05 mg/kg, n=29; 0.2 mg/kg, n=32; and 0.4 mg/kg, n=32) the corresponding treatment groups were relatively balanced with regard to the baseline characteristics. Table S1 shows baseline characteristics for the ITT population all doses pooled.

Table S1 Demographic and baseline characteristics (ITT population, all doses pooled)

Demographic		**N=93**
Sex, n (%)	Female	33 (35.5)
	Male	60 (64.5)
Age, years, (n (%)	1 to <2	16 (17.2)
	2 to <6	77 (82.8)
Race, n (%)	Black	17 (18.3)
	Non-Black	76 (81.7)
Type of hypertension, n(%)	Systolic + diastolic	49 (52.7)
	Diastolic only	20 (21.5)
	Systolic only	21 (22.6)
	None[a]	3 (3.2)
Systolic blood pressure	Mean (SD), mmHg	112 (8.7)
Diastolic blood pressure	Mean (SD), mmHg	70 (8.8)
On antihypertensive therapy prior to study entry	n (%)	39 (41.9)
Source of hypertension, n (%)	Primary	22 (23.7)
	Secondary	71 (76.3)

[a] The sponsor used the same program as the IVRS in constructing the demography tables, but the site used a different calculation for study entry hence some subjects appeared to not have met the criteria. The 'no hypertension group' represents an apparent difference in the site's determination of the 95th percentile (using the charts supplied in the protocol and the program calculation) versus the IVRS program..

Note: Type of hypertension was based on blood pressure at Visit 3 randomization and is defined as diastolic hypertension ≥95th percentile and systolic hypertension ≥95th percentile.

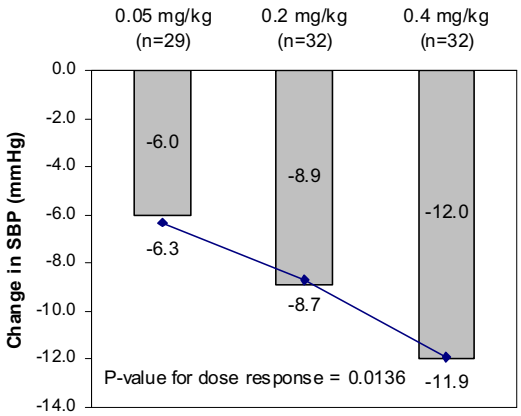
Note: Data for the 'source of hypertension' and 'presence of renal disease' categories were created from a review of the medical history by the study physician.

A total of 69 children (74%) had renal disease at baseline, which included nephrotic syndrome, congenital cystic renal diseases, dysplastic disorders, hemolytic uremic syndrome,

and others. Baseline mean serum estimated glomerular filtration rate (eGFR) was 121.3 ml/min (baseline range 37 to 462 ml/min) and 22 children had below normal eGFR at baseline (normal range 80 to 125 ml/min). Median urine baseline P/C ratio was 0.3 (range 0.1 to 59.5) and median A/C ratio was 36 mg/g creatinine (range 3 to 5327 mg/g creatinine), normal is 0 to 30 mg/g creatinine.

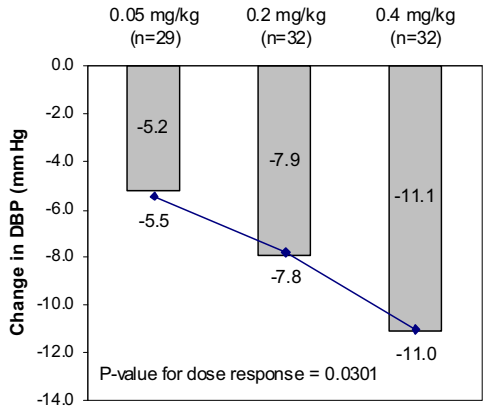
Efficacy and pharmacokinetic results: SBP declined monotonically across the 3 candesartan dose levels by 6 to 12 mmHg, a decline that was significantly related to candesartan dose, Figure S1. Similarly, DBP declined by 5 to 11 mmHg in a significant dose-related fashion, Figure S2.

Figure S1 **Means and dose-response line for changes from baseline to Week 4/LOCF in SBP (ITT population)**



Note: Numbers inside the bars are the raw means. The connected dots and the values that are provided below the dots, represent the dose-response line assuming the weight effect is proportional to the number of subjects in the upper weight panel.

Figure S2 **Means and dose-response line for changes from baseline to Week 4/LOCF in DBP (ITT population)**



Note: Numbers inside the bars are the raw means. The connected dots and the values that are provided below the dots, represent the dose-response line assuming the weight effect is proportional to the number of subjects in the upper weight panel.

After 4 weeks of dosing, antihypertensive response rates increased monotonically with increasing dose (28%, 50%, and 66%, respectively) for the 0.05 mg/kg, 0.2 mg/kg, and 0.4 mg/kg dose groups.

Blood pressure reductions were evident across subgroups indicating an antihypertensive effect in Black children, in children with secondary hypertension, children with both diastolic/systolic hypertension, children with renal disease, in both the younger and older children (1 to 2 years vs 2 to 6 years of age), and children in both geographical regions (US/Puerto Rico and Europe).

The antihypertensive effect of candesartan was maintained with long-term dosing and 54% of subjects were 'controlled' (responders) at the end of 1 year of treatment.

With multiple dosing, the plasma candesartan levels were dose related.

The single dose PK substudy indicated that there was no correlation between AUC or C_{max} and age (correlation –0.392, p=0.2627 for AUC and correlation –0.437, p=0.2064 for C_{max}) or body weight (correlation –0.392, p=0.2627 for AUC and correlation -0.437, p=0.2064 for C_{max}) and the. PK profile was similar to that previously described for older children and adults.

Safety results

Overall, administration of candesartan for up to 56 weeks at a mean dose of 0.2 mg/kg was generally well tolerated (2 subjects discontinued because of AEs). The most common AEs included: pyrexia (41%), cough (38%), upper respiratory tract infection (23%), nasopharyngitis (17%), rhinorrhea (15%), and diarrhea (15%). (Most of the subjects with pyrexia had other associated illnesses, eg, pharyngolaryngeal pain, nasal congestion, cough, sinus congestion, upper respiratory infection).

Two subjects were discontinued from the study prematurely due to AEs: 1 child died on Day 200 of treatment from an underlying disorder (chronic glomerulonephritis and progressive renal insufficiency); the other child, who had moderate abdominal pain and fatigue that started on Day 11 of treatment, was discontinued from treatment on Day 37; this child did not enter the open-label period of the study. A total of 14 children had SAEs but these largely reflected the consequence of co-morbid illnesses and none was considered by the investigators to be causally related to study medication.

There were no notable changes in laboratory or other safety measures. Estimated eGFR declined by 5.6 ml/min during the first 4 weeks but was relatively stable thereafter over the 1-year, follow-up period.

The median A/C ratio declined by 38% (25th, 75th percentiles: –61, 25) after 4 weeks treatment with candesartan. The decline appeared dose related and was still evident at Week 56 (median decline 31%; 25th, 75th percentiles –63, 36). In subjects with a baseline A/C ratio >30 mg/g creatinine, the median A/C ratio declined 57% (25th, 75th percentile –72 , –3) after 4 weeks treatment; the decline at Week 56 was 59% (25th, 75th percentiles –85, –26).

There was no change in P/C ratio with candesartan treatment with all subjects considered; there was, however, a 33 median % decline (25th, 75th percentiles: -49, 0) among subjects with a baseline P/C ratio >0.2.

Conclusion(s)

In hypertensive children 1 to <6 years of age, candesartan significantly lowers SBP and DBP in a dose-related fashion over a dose range of 0.05 mg/kg to 0.4 mg/kg.

A candesartan antihypertensive effect is apparent within 1 to 2 weeks of initiating treatment and a nearly full effect is apparent within about 4 weeks.

The antihypertensive effect is not notably modified by age, gender, race, weight, or secondary hypertension.

An antihypertensive effect can be maintained long term (1 year).

The PK profile of candesartan (suspension formulation) in children 1 to <6 years of age is similar to that in older children and adults (tablet formulation). There is no correlation between C_{max} or AUC and age or body weight.

With multiple dosing, candesartan plasma concentrations are dose related.

In children with albuminuria (A/C ratio >30 mg/g creatinine), candesartan treatment is associated with a reduction in albuminuria which appears to be dose related.

Long-term administration of candesartan for up to 56 weeks in this pediatric hypertensive population was generally well tolerated – the same safety oversight vigilance recommended for hypertensive adults is relevant for hypertensive children.

Date of the report

25 March 2009

Table Protocol amendments

Number (date of internal approval)	Key details of amendment	Reason for amendment
Amendments made after the start of subject recruitment		
Amendment 1 20 February 2006	Protocol synopsis. Protocol Section 3.1 This study is planned for approximately 40 centers located in United States, Puerto Rico, and Europe.	Centers in Europe have been added to reach enrollment goals.
	Protocol synopsis, Section 2.2 bullets 2 and 3, Section 4.2, Section 4.6 Method of assessment. Section 4.6.2, Section 6.2.2, and Section 6.4.2. The dose response relationship of candesartan for the change in trough DBP. The mean change in trough SBP and DBP for candesartan. The slope for change from baseline is determined for DBP.	Supine blood pressures will not be measured or analyzed, except for children who are unable to sit.
	Protocol synopsis, Protocol Section 3.1, Sections 3.3.1, and 6.4.3. Deleted: Black and non-Black subjects will be recruited to meet the overall program objective of 40-60% Black representation.	The required percentage of black subjects for this Pediatric Program was fulfilled through Study 261.
	Table 2 Table of procedures, Section 4.2 Screening at demographic measurement, and Section 4.77. At Visit 3, only urine chemistry will be performed. Measurement of head circumference in children ≤36 months at study entry.	Clarification of laboratory testing Clarification of age of children when measuring head circumference
	Protocol Section 3.2.2 Dose rationale Weight panels are 10 to <25 kg and 25 to ≤40 kg	Clarification of weight panel division
	Protocol Section 3.3.2 Inclusion criteria. Section 4.6.1 Calculation of BP values. The BP values that determine eligibility at screening and randomization are based on the average of 3 SBP measurements within a 7 mmHg range (consecutive or non-consecutive) in the arm with the higher BP measurement. Up to a maximum of 6 BP measurements may be obtained to achieve the 3 SBP values within the 7 mmHg range. The time period between SBP readings must not be less than 1 minute.	Clarification of inclusion criteria: the mean of 3 BP measurements may be calculated from 3 consecutive or non-consecutive measurements in order for the subject to qualify for the study.
	Section 3.3.3 Exclusion criteria Exclusion 6. Estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m^2 for non-transplant patients and <40 ml/min/1.73m^2 for transplant patients based on the Schwartz Formula (Schwartz et al 1987) Exclusion 7. ….eGFR ≥40 ml/min/1.73m^2, 3)	A reduction in the lower limit of eGFR for inclusion will allow additional patients to qualify for the study and subjects with lower eGFR at entry may benefit from the protective effects of candesartan.

Number (date of internal approval)	Key details of amendment	Reason for amendment
	Section 3.3.5.2 Procedures for discontinuation If discontinued after randomization and prior to Visit 7, then complete Visit 7 procedures. If discontinued after Visit 7 and prior to Visit 15, then complete Visit 15 procedures. For those subjects participating in the Medication Adherence Sub-Study, collect the MEMS cap from subject/parent, distribute and collect psychosocial surveys from subject/parent (Appendix I) and Investigator completes Nonadherence Risk Survey.	Clarification of study discontinuation procedures.
	Section 3.4.1.3 Labelling	Clarification of labelling differences for the United States, Puerto Rico, and Europe.
	Section 4.7.8 Medication adherence, Sections 6.2.4, and 6.4.5 New text: This portion of the study is managed by Johns Hopkins University of Baltimore Maryland, US. Medication Adherence Sub Study is optional in Europe. Prevalence of poorly adherent patients with knowledge or psychosocial impairments will be identified using a Nonadherence Risk Survey. In US & PR: electronic monitor data, patient self-report, medication residuals; In Europe: electronic monitor data, medication residuals.	Clarification of the party responsible for the Medication Adherence substudy and that the study is optional for the countries in Europe. Clarification of endpoint for Medication Adherence substudy. This is a clarification of the analysis endpoints.
	Section 4.7.8.1 Method of Assessment Added additional text In Europe, data from the MEMS caps will be retrieved at the end of the trial and analyzed to determine an estimate of subject adherence with the recommended medication administration regimen. Adherence will be determined by evaluating the frequency of medication syringe removal from the monitored storage container. Telephone interviews will not be conducted with European participants.	To clarify the variances in the substudy procedures for participating European centres. Since the Parenting Stress Index-Short Form is only validated in the English language, and since some of the European centers want to participate, this assessment tool was deleted from the substudy.
	Section 5 Data management The top original and first yellow copy of each CRF can go to the CRO or the Marketing Company. Dictionary coding used the most current version of MedDRA and AZDD.	Several Marketing Companies in Europe are supporting the study, this is a clarification of the flow of data. Now using the AstraZeneca Drug Dictionary (AZDD) to code medications.
Amendment 2 6 July 2007	Section 6.6 Interim analysis No interim analyses are planned. However, the efficacy data from the 4-week, double-blind period will be analyzed once all patients have completed this period, these data are cleaned, and the corresponding database is locked.	This amendment provides the authority to analyze the double-blind, dose-response phase of the trial without waiting until the long-term, open-label phase of the study completes. These data are necessary to support the rationale for the development of an age-appropriate (liquid) marketable formulation for pediatric patients.
Amendment 3 12 February 2008	Safety sections and Table 2 Table of procedures Echocardiograms are added. ECHO performed as soon as possible during any open-label phase visit (V7 to V15) and at study completion/discontinuation. If an ECHO was performed within the last 3 months, it does not need to be repeated at study completion/discontinuation.	Echocardiography is added following recommendations from the Paediatric Committee (PDCO) at the European Medicines Agency (EMEA).

[a] All protocol amendments were approved within AstraZeneca Marketing Companies before being implemented.

BP Blood pressure; CRF Case report form; CRO Contract Research Organization; ECHO Echocardiograph; eGFR Estimated glomerular filtration rate; MedDRA Medical Dictionary of Regulatory Activities; MEMS Medication Event Monitoring System; DBP Diastolic blood pressure; SBP Systolic blood pressure

Investigational Site(s) – D2451C00002

Country	Centre address
United States of America	Jackson Memorial Hospital Pediatric Dialysis Unit 1611 NW 12th Ave Miami, FL 33136
	* Sutter North Medical Foundation 440 Plumas Blvd Yuba City, CA 95991
	* Stanford Univ. Medical Center 300 Pasteur Ave Pediatric Nephrology Stanford, CA 94305-5208
	Erlanger Health System Hypertension Management Center 960 E Third St, Chattanooga, TN 37403
	University of Texas Health Science Center Children's Kidney Center 7703 Floyd Curl Drive MC 7813 San Antonio, TX 78229-3900
	Little Rock Pediatric Clinic 7 Mavis Circle Mabelvale, AR 72103
	Columbus Children's Hospital 555 S 18th St., Columbus, OH 43205
	University Hospitals of Cleveland 11100 Euclid Ave., Cleveland, OH 44106
	University Pediatric Hosp Pediatric Renal Center PR Medical Center Bo. Monacillos San Juan, PR 00935

Country	Centre address
	* Spectrum Health Hospitals Cook Research Dept 333 Bostwick NE, Ste 6150 Grand Rapids, MI 49503
	* Medical University of South Carolina Clinical Trials Center 96 Jonathan Lucas St, Charleston, SC 29425
	NW Pediatric Kidney Specialists, LLC. 501 N Graham, Portland, OR 97227
	Southeast Texas Clinical Research Center 2693 North Street Beaumont, TX 77702
	* University of Michigan - Pediatric Nephrology Mott F6865 / Box 0297 1505 Simpson Rd East Ann Arbor, MI 48109-0297
	UCSF Medical Center Pediatric Nephrology 533 Parnassus Ave San Francisco, CA 94143-0748
	* Children's Research Institute Dept of Nephrology 111 Michigan Ave, NW Washington, DC 20010
	Hope Children's Hospital Nephrology & Hypertension Consultants, Inc 1550 Northwest Hwy, Park Ridge, IL 60068
	* College of Medicine Department of Pediatrics PO Box 100296 1600 SW Archer Rd, Gainesville, FL 32610

Country	Centre address
	Neufeld Medical Group, Inc. 8733 Beverly Blvd, Los Angeles, CA 90048
	University of Texas Health Science Center Pediatric Nephrology & Hypertension 6431 Fannin St, Houston, TX 77030
	* Loma Linda School of Medicine Dept of Pediatrics Coleman Pavilion 11175 Campus St, Loma Linda, CA 92350
	* University of Louisville 231 E Chestnut N-97 Louisville, KY 40202
	University of Alabama at Birmingham Pediatric Nephrology 1600 7th Ave S ACC 516 Birmingham, AL 35233
	* St Joseph Children's Hospital 703 Main Street Paterson, NJ 07503
	Duke Univ. Medical Center Pediatric Nephrology Children's Health Center 2100 Erwin Road Durham, NC 27710
	Nemours Children's Clinic 496 S. Delaney Ave, Orlando, FL 32801
	Children's Hospital of Michigan 4th Floor Carls Bldg, Nephrology 3901 Beaubien Blvd Detroit, MI 48201
	* Pediatric Heart Clinic 864 Central Blvd., Brownsville, TX 36608

Country	Centre address
	Childrens Kidney Specialists 100 E. Idaho, Boise, ID 83712
	* University of Michigan Health System Womens L1242, Box 0204 1500 E. Medical Center Drive Ann Arbor, MI 48109
Belgium	Kindernefrologie, Pediatrie K6 UZ Gent De Pintelaan 185 Gent B-9000 Belgium
	Dept. Pediatrie UZ Antwerpen Wilrijkstraat 10 Edegem B-2650 Belgium
Denmark	* University Hospital Rigshospitalet Blegdamsvej 9 Kobenhavn DK-2100 Denmark
	Paediatrisk Afdeling A Skejby Hospital Brendstrupgårdsvej 100 Århus N DK-8200 Denmark
Germany	University Children's Hospital Center for Pediatrics & Adolescent Medicine Dept. of Pediatric Nephrology Im Neuenheimer Feld 153 Heidelberg D- 69120 Germany

Country	Centre address
	University Hospital Giessen and Marburg GmbH Mother and Child Centre Medical Centre for Children and Youth KKFP Baldingerstr. Marburg D-35043 Germany
	Charite Children's Hospital - Campus Virchow Dept. of Pediatric Nephrology Augustenburger Platz 1 Mittelalle 8 Berlin D-13353 Germany
	University Hospital Hamburg-Eppendorf University Children's Hospital Dept. of Pediatric Nephrology (N-23) Martini Strasse 52 Hamburg D-20246 Germany
	* University Hospital Essen Hosp. For Pediatrics & Adolescent Medicine Dept of Pediatric Nephrology Hufelandstr.55 Essen D-45122 Germany
	* Dr. von Haunersches Kinderspital der Universitat Munchen Lindwurmstr. 4 Munchen D-80337 Germany
	Universitatsklinikum Erlangen Klinik fur Kinder and Jugendliche LoschgestraBe 15 Erlangen D-91054 Germany

Country	Centre address
	Universitatsklinikum Freiburg Zentrum fur Kinderheilkunde und Jugendmedizin Mathildenstrasse 1 D-79106 Freiburg, Germany
	Universitats-Kinder und Jugendklinik Rembrandtstr. 17 – 18 Rostock D-18075 Germany
Poland	* Dept of Nephrology, Kidney Transplantation and Hypertension Children Memorial Health Institute Al. Dzieci Polskich 20 Warsau 04-730 Poland
	* 1st Clinic of Pediatrics Pomeranian Medical University ul. Unii Lubelskiej 1 Szczecin 71-252 Poland
	Uniwersytecki Szpital Dzieciecy w Krakowie Wielicka 265 Krakow 30-663 Poland
	Department Paediatric Nephrology Gdańsk University Medical School ul.Dębinki 7 Gdańsk 80-211 Poland
United Kingdom	Paediatric Nephrology Great Ormond Street Children's Hospital Great Ormond Street London WC1N 3JH Great Britian

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	Renal Unit Royal Manchester Children's Hospital Hospital Road Pendlebury Manchester M27 4HA Great Britian
Italy	IRCCS Ospedale Maggiore Policlinico-Mangiagalli Unit of Pediatric Nephrology Dialysis & Transplantation Dept. of Pediatrics Via Commenda 9 Milano 1-20122 Italy
	G. Gaslini Institute Nephrology Unit Largo 6, Gaslini 5 Genoa 5-16148 Italy
	Ospedale Pediatrico Bambino Gesu Div. Di Nefrologia e Dialisi Piazza S. Onofrio 4 Italy
	University of Padua Pediatric Department Nephrology, Dialysis and Transplant Unit Via Giustiniani 3 Padova I-35128 Italy
Ukraine	City of Children Clinical Hospital #7 Pidvysotskogo str. 4A Kyiv UA-01103 Ukraine

Country	Centre address
	Crimean Republican Children Clinical Hospital Titova str 77 Simferopol Crimea UA-95034 Ukraine
France	Hôpitaux Universitaires de Strasbourg Hôpital de Hautepierre Service de Pédiatrie 1 Avenue Moliere Strasbourg 67098 France
	* Hôpital Edouard-Herriot 5 Place D'Arsonval Pavillion S (Pediatrie) 69437 Lyon cedex 03 France

* = No subjects enrolled