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Clinical Development

VAL489/Valsartan

Clinical Trial Protocol CVAL489K2306

A 6 week, randomized, multicenter, double-blind, double-dummy study to evaluate the dose response of valsartan on blood pressure reduction in children 1-5 years old with hypertension, with or without chronic kidney disease, followed by a 20 week open-label titration phase

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Table of contents

Table of contents 2
List of tables 5
List of figures 5
List of abbreviations 6
Glossary of terms 9
Protocol synopsis 10
1 Introduction 16
1.1 Background 16
1.2 Purpose 17
2 Study objectives 17
2.1 Primary objectives 17
2.2 Secondary objectives 17
2.3 Exploratory objectives 18
3 Investigational plan 18
3.1 Study design 18
3.2 Rationale of study design 21
3.3 Rationale of dose/regimen, duration of treatment 22
3.4 Rationale for choice of comparator 22
3.5 Purpose and timing of interim analyses/design adaptations 22
3.6 Risks and benefits 22
4 Population 23
4.1 Inclusion criteria 24
4.2 Exclusion criteria 24
5 Treatment 26
5.1 Protocol requested treatment 26
5.1.1 Investigational treatment 26
5.1.2 Additional study treatment 27
5.2 Treatment arms 27
5.3 Treatment assignment, randomization 27
5.4 Treatment blinding 28
5.5 Treating the patient 28
5.5.1 Patient numbering 28
5.5.2 Dispensing the investigational treatment 28
5.5.3 Handling of study treatment 29
5.5.4 Instructions for prescribing and taking study treatment 29
5.5.5 Permitted dose adjustments and interruptions of study treatment 30

[redacted]

5.5.6 Rescue medication 30
5.5.7 Concomitant treatment 30
5.5.8 Prohibited treatment 31
5.5.9 Discontinuation of study treatment and premature patient withdrawal 31
5.5.10 Emergency breaking of treatment assignment 33
5.5.11 Study completion and post-study treatment 34
5.5.12 Early study termination 34
6 Visit schedule and assessments 34
6.1 Information to be collected on screening failures 37
6.2 Patient demographics/other baseline characteristics 37
6.3 Treatment exposure and compliance 38
6.4 Efficacy 38
6.4.1 Office blood pressure 38
6.4.2 Appropriateness of efficacy assessments 39
6.5 Safety 39
6.5.1 Physical examination 39
6.5.2 Vital signs 39
6.5.3 Height, weight, and head circumference 39
6.5.4 Laboratory evaluations 40
6.5.5 Electrocardiogram (ECG) 41
6.5.6 Pregnancy and assessments of fertility 42
6.5.7 Appropriateness of safety measurements 42
6.6 Other assessments 42
6.6.1 Resource utilization 42
6.6.2 Health-related Quality of Life 42
6.6.3 Pharmacokinetics 42
6.6.4 Pharmacogenetics/pharmacogenomics 42
6.6.5 Other biomarkers 42
7 Safety monitoring 42
7.1 Adverse events 42
7.2 Serious adverse event reporting 44
7.3 Liver safety monitoring 45
7.4 Pregnancy reporting 45
7.5 Prospective suicidality assessment 46
8 Data review and database management 46
8.1 Site monitoring 46

[redacted]

8.2 Data collection 46
8.3 Database management and quality control 46
8.4 Data Monitoring Committee 47
8.5 Adjudication Committee 47
9 Data analysis 47
9.1 Analysis sets 47
9.2 Patient demographics and other baseline characteristics 48
9.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance) 48
9.4 Analysis of the primary variable(s) 48
9.4.1 Variable 48
9.4.2 Statistical model, hypothesis, and method of analysis 49
9.4.3 Handling of missing values/censoring/discontinuations 49
9.4.4 Supportive analyses 49
9.5 Analysis of secondary variables 49
9.5.1 Key secondary variables 49
9.5.2 Efficacy variables 49
9.5.3 Safety variables 50
9.5.4 Resource utilization 50
9.5.5 Health-related Quality of Life 50
9.5.6 Pharmacokinetics 50
9.5.7 Pharmacogenetics/pharmacogenomics 50
9.5.8 Biomarkers 50
9.5.9 PK/PD 50
9.6 Interim analyses 50
9.7 Sample size calculation 50
9.8 Power for analysis of key secondary variables 51
9.9 Interim analyses 51
10 Ethical considerations 51
10.1 Regulatory and ethical compliance 51
10.2 Informed consent procedures 51
10.3 Responsibilities of the investigator and IRB/IEC 51
10.4 Publication of study protocol and results 52
11 Protocol adherence 52
11.1 Protocol Amendments 52
12 References 53
13 Appendix 1: Clinically notable laboratory values 55

[redacted]

Appendix 2: Pediatric blood pressure tables and growth charts....56
Special methods and scales....57
BP Levels for girls by Age and Height Percentile (1-6 years old)....61
BP Levels for boys by Age and Height Percentile (1-6 years old)....63

List of tables

Table 5-1 Prohibited treatment....31
Table 6-1 Assessment schedule....36

List of figures

Figure 3-1 Study design....19
Figure 3-2 Blood pressure cuff size....21

[redacted]

List of abbreviations

ACE	Angiotensin Converting Enzyme
ACEi	Angiotensin Converting Enzyme Inhibitor
ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase / Serum Glutamic Pyruvic Transaminase / SGPT
ANOVA	Analysis of Covariance
ARB	Angiotensin Receptor Blocker
AST	Aspartate Aminotransferase / Serum Glutamic Oxaloacetic Transaminase / SGOT
B-hCG	Beta human Chorionic Gonadotrophin
BP	Blood Pressure
CHMP	EMA Committee for Medicinal Products
CKD	Chronic Kidney Disease
CO_2	Carbon Dioxide
COX-2	Cyclooxygenase-2
CRF	Case Report/Record Form
CRO	Contract Research Organization
CPO	Country Pharma Organization
CSR	Clinical Study Report
CTH	Clinical Trial Head
DBP	Diastolic Blood Pressure
dL	Deciliter
DRI	Direct Renin Inhibitor
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
GFR	Glomerular Filtration Rate
EMA	European Medicines Agency
FAS	Full Analysis Set
GCP	Good Clinical Practice

[redacted]

HCTZ	Hydrochlorothiazide
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IIS	Integrated Information Sciences
IRB	Institutional Review Board
IRT	Interactive Response Technology
kg	Kilograms
L	Liter
LFT	Liver Function Test
LOCF	Last Observation Carried Forward
MAO	Mono Amine Oxidase
MAX	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
min	Minute
mL	Milliliter(s)
mmHg	Millimeters of Mercury
mmol	Millimole(s)
MSBP	Mean Systolic Blood Pressure
MDBP	Mean Diastolic Blood Pressure
NSAID	Non-Steroidal Anti-Inflammatory Drug
NYHA	New York Heart Association
OFAS	Open-label Full Analysis Set
OSAF	Open-label Safety
PDCO	Paediatric Committee
PPS	Per Protocol Set
RAAS	Renin Angiotensin Aldosterone System
RAN	Randomized set
SAE	Serious Adverse Event
SAF	Safety Analysis Set

[redacted]

SBP	Systolic Blood Pressure
SGOT	Serum Glutamic Oxaloacetic Transaminases / Alanine Aminotransferase / AST
SGPT	Serum Glutamic Pyruvic Transaminases / Aspartate Aminotransferase / ALT
SUSAR	Suspected Unexpected Serious Adverse Reaction
UACR	Urine Albumin Creatinine Ratio
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

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Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IVR system
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later
Study drug/ treatment	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any control drugs
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

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Protocol synopsis

Protocol number	CVAL489K2306
Title	A 6 week, randomized, multicenter, double-blind, double-dummy study to evaluate the dose response of valsartan on blood pressure reduction in children 1-5 years old with hypertension, with or without chronic kidney disease, followed by a 20 week open-label titration phase
Brief title	Dose response study of valsartan in children (1-5 years) with hypertension, with or without chronic kidney disease
Sponsor and Clinical Phase	Novartis
Investigation type	• VAL489 (Valsartan) 0.25 mg/kg or 4 mg/kg and matching placebo • VAL489 (Valsartan) 4 mg/kg
Study type	Interventional
Purpose and rationale	This study is part of the European Diovan® pediatric program and is conducted at the request of the EMA/Pediatric Committee (PDCO). Two previous trials, using valsartan, have been conducted in hypertensive children between 6 months and 5 years with mixed results. The EMA Committee for Medicinal Products for Human Use (CHMP) emphasized that a clinical need in this age group exists and that it would be relevant to conduct a new study (Section 3.2). The purpose of this study is to establish a dose response for valsartan solution in children 1-5 years old with hypertension (mean systolic blood pressure ≥ 95th percentile), with or without chronic kidney disease (CKD). A sub-analysis will be performed to study the safety and tolerability of valsartan in children with CKD. An open-label phase has been added to study the safety of valsartan. The effects of valsartan on renal function and proteinuria will also be evaluated in CKD patients.
Primary Objective(s) and Key Secondary Objective	Primary: • To evaluate if a dose dependent reduction in mean systolic blood pressure (MSBP) exists when comparing two doses of valsartan solution (0.25 mg/kg and 4 mg/kg) over a 6 week period in children 1-5 years old with hypertension (MSBP ≥ 95th percentile for age, gender and height), with or without CKD. Secondary: • To assess the efficacy of valsartan in reducing the mean diastolic blood pressure (MDBP) in children with hypertension. • To assess the efficacy of valsartan in controlling the MSBP and MDBP in children with hypertension. The target mean BP is <90th percentile for age, gender and height. • To assess the safety and tolerability profile of valsartan in children with

	hypertension, with or without CKD. • To assess the effect of valsartan on proteinuria and eGFR in a subset of children with hypertension and CKD
Secondary Objectives	Refer to above
Study design	This is a 6 week, randomized, multicenter, double-blind, double-dummy study to evaluate the dose response of valsartan solution on blood pressure reduction in children 1-5 years old with hypertension, with or without chronic kidney disease, followed by a 20 week open-label phase with an optional titration period. Period 1 is a 6 week double-blind dose- ranging period to ensure that the maximum antihypertensive effect of valsartan will be reached. Period 2 is an open-label optional titration phase, where the safety of valsartan can be assessed including potential effects on proteinuria. Patients entering the study receiving background antihypertensive treatments may continue on these medications as long as they meet the eligibility criteria for MSBP (≥ 95th percentile). The background therapy and dose should remain unchanged for the duration of the study. No patients will be permitted in the study with background RAAS blocker therapy (ARBs, ACEi, DRIs). This study consists of three periods: A Screening period of up to 28 days Period 1: A six-week randomized, double-blind, double-dummy dose-ranging period consisting of 2 valsartan dose groups (0.25 mg/kg and 4 mg/kg), and randomization will be 1:1. Period 2: A 20 week open-label titration phase where all patients will start with 1 mg/kg valsartan for four weeks then be optionally titrated every four weeks. Patients may receive up to 4 mg/kg of valsartan.
Population	The study population will consist of a representative group of 130, male and female children age 1-5 years by visit 2. All patients must have a history of hypertension defined as a MSBP ≥ 95th percentile to be eligible for randomization into this study. Approximately 50 sites are planned for this study. A total of 200 patients will be screened to randomize 130 patients with an anticipated screen failure rate of 35%. A drop out rate of 10% during the double-blind period is expected. A total of 116 patients are expected to complete the double-blind period and enter the open-label period. Patients will be stratified based on CKD status (yes /no). At least 50% of patients enrolled will be CKD patients. CKD patients must have a documented history of CKD.
Inclusion criteria	1. Written informed consent must be obtained before any assessment is performed. Parent(s)/guardian(s) have to provide consent in writing (written informed consent) after the purpose and nature of the study has been clearly explained to them.

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	2. Male or female, 1 to 5 years at baseline (visit 2), with a documented diagnosis of hypertension (National High Blood Pressure Education Program 2004) 3. CKD patients must be defined as any of the following criteria (Hogg et al 2003) (At least 50% of enrolled patients will be CKD-patients): a. Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by one or more of the following features: • Abnormalities in the composition of urine • Abnormalities in imaging tests • Abnormalities on kidney biopsy b. Estimated GFR <60 mL/min/1.73m2 (calculated by Modified Schwartz Formula) for ≥3 months, with or without the other signs of kidney damage described above. 4. MSBP (mean of 3 measurements) must be ≥95th percentile, and ≤25% above the 95th percentile, for age, gender and height, at baseline (visit 2) (Appendix 2), by office automatic blood pressure monitor and cuff, provided by the Sponsor. Confirmation of MSBP ≥95th percentile must be made using the auscultatory blood pressure method. 5. Able to swallow the valsartan solution 6. Body weight must be ≥8 kg and ≤40 kg at baseline 7. Must be able to safely washout prior ARB, ACEi and DRI therapy (if applicable) and other antihypertensive therapy (if applicable).
Exclusion criteria	1. Any clinically significant physical abnormality or clinically relevant abnormal laboratory values (other than those relating to renal function) obtained at the screening visit (Visit 1), including the following: a. AST/SGOT or ALT/SGPT >3 times the upper limit of the reference range. Patients known to have active or chronic hepatitis will be excluded. b. Total bilirubin >2 times the upper limit of the reference range c. Estimated Glomerular Filtration Rate [eGFR] <30 mL/min/1.73m² (calculated using Modified Schwartz Formula) d. WBC count <3000/mm³ e. Platelet count <100,000/mm³ f. Serum potassium >5.3 mmol/L g. Hemoglobin <9 g/dL 2. Uncontrolled diabetes mellitus, as defined by the investigator 3. Unilateral, bilateral and graft renal artery stenosis 4. Current diagnosis of heart failure (NYHA Class II-IV) 5. Patients taking any of the following concomitant medications following screening: a. RAAS blockers other than study drug b. Lithium

[redacted]

	c. Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels d. Non-steroidal anti-inflammatory drugs (NSAIDS), including selective COX-2 inhibitors, acetylsalicylic acid >3g/day, and non-selective NSAIDs (paracetamol/acetaminophen is permitted) e. Antidepressant drugs in the class of MAO inhibitors (e.g. phenelzine) f. Chronic use of stimulant therapy for ADD/ADHD 6. Patients with ECG abnormalities associated with left ventricular hypertrophy are permitted to enroll. Patients who demonstrate clinically significant ECG abnormalities such as concurrent potentially life threatening arrhythmias or symptomatic arrhythmias are excluded, as are patients with second or third degree heart block without a pacemaker. 7. Patients who have coarctation of the aorta with a gradient of ≥30 mmHg 8. Previous solid organ transplantation except renal transplantation. Renal transplant must have occurred at least 1 year prior to enrollment. Patient must be on stable doses of immunosuppressive therapy and deemed clinically stable by the investigator. Stable doses of immunosuppressive therapy are defined as no change in frequency or total daily doses of immunosuppressive therapy for at least two months prior to screening. 9. Patients known to be positive for the human immunodeficiency virus (HIV) 10. Any clinically significant medical condition that would put the patient at risk of experiencing an adverse event associated with the expected pharmacodynamic effects of the study drug 11. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of the study drug including, but not limited to, any of the following: a. History of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection. b. Currently active or previously active inflammatory bowel disease during the 12 months prior to Visit 1. c. Patients known to have currently active gastritis, duodenal or gastric ulcers, or gastrointestinal/rectal bleeding during the 3 months prior to Visit 1. d. Patients known to have active pancreatic injury, pancreatitis or evidence of impaired pancreatic function/injury as indicated by abnormal lipase or amylase. e. History of hepatic encephalopathy, a history of esophageal varices, or a history of porto-caval shunt. f. Current obstruction of the urinary tract or difficulty in voiding due to mechanical or inflammatory conditions which is likely to require intervention during the course of the study or is regarded as clinically meaningful by the investigator. 12. Known or suspected contraindications to the study drug, including

[redacted]

	severe hepatic impairment, biliary cirrhosis, cholestasis and history of allergy to other ARBs or to ACEIs and/or DRIs 13. History of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin 14. Participation in any investigational drug study within 30 days prior to screening or within 5 elimination half-lives of the study drug prior to screening, or whichever is longer. 15. History of hypersensitivity to the study drug or to drugs of similar chemical classes. 16. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency since the study drug solution contains sucrose. If there is any question that the patient will not reliably comply, they should not be entered in the study.
Investigational and reference therapy	Period 1: VAL489 (Valsartan) 0.25 mg/kg or 4 mg/kg VAL489 (Valsartan) 0.25 mg/kg or 4 mg/kg matching placebo Period 2: VAL489 (Valsartan) 1 mg/kg, optional titration 2 mg/kg, 3 mg/kg and 4 mg/kg (max dose).
Efficacy assessments	Mean office blood pressure (mean of 3 measurements)
Safety assessments	Safety and tolerability assessments: Adverse event assessment Hematology laboratory assessments are performed at Visits 1, 2, 5, 8, 9, 10 and 11. Hematology: Red blood cell count, hemoglobin, hematocrit, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelet count. Complete blood chemistry laboratory assessments are performed at Visits 1, 2, 5, 8 and 11. Abbreviated blood chemistry laboratory assessments are performed at Visits 9 and 10. Complete blood chemistry: urea, creatinine, non-fasting glucose, total bilirubin, AST/SGOT, ALT/SGPT, ALP, sodium, potassium, bicarbonate (total CO_2), chloride, calcium, phosphorous, total protein, albumin, uric acid, cholesterol, triglycerides and eGFR Abbreviated blood chemistry: urea, creatinine, sodium, potassium, bicarbonate (total CO_2) and eGFR Cystatin C is obtained only for CKD patients at Visits 2, 5, 10 and 11. Urine Albumin Creatinine Ratio (UACR) (in CKD patients only) at Visits 2,

[redacted]

	5, 10, and 11. eGFR For all patients eGFR will be calculated using the Modified Schwartz formula For CKD patients the eGFR will also be calculated using the cystatin C value. Urine dipstick at Visits 1, 2, 5 and 11. Urinalysis done locally by dipstick: glucose, protein, bilirubin, ketones, leukocytes, blood Electrocardiogram (ECG) at Visits 1, 5 and 11.
Other assessments	Not applicable
Data analysis	The primary objective is to evaluate if a dose dependent reduction in MSBP exists when comparing two doses of valsartan solution (0.25 mg/kg and 4 mg/kg) over a 6 week period in children 1-5 years old with hypertension (MSBP ≥ 95th percentile for age, gender and height), with or without CKD. The null hypothesis is that there is no treatment difference in the reduction of MSBP between dose groups 0.25 mg/kg and 4 mg/kg. The alternative hypothesis is that there is a difference between dose groups 0.25 mg/kg and 4 mg/kg. The comparison will be tested at a two-sided significance level of 0.05. The change from baseline in MSBP at Week 6 endpoint during double-blind period will be analyzed using an analysis of covariance model (ANCOVA) with treatment and CKD strata as factors and baseline MSBP as a covariate for the FAS population. The secondary variables are change from baseline in mean diastolic blood pressure (MDBP) at Week 6 endpoint and end of study; percentage of patients achieving MSBP < 90th percentile for age, gender and height at Week 6 endpoint and end of study; UACR response (defined as % change from baseline in UACR ≤ 25%) at Week 6 endpoint and end of study. The sample size of 116 completed patients is calculated based on the primary efficacy variable, change from baseline in mean systolic blood pressure, and a standard deviation of 11 mmHg (based on previous data) is used. The sample size is calculated to ensure at least 80% power to detect statistical significance for the comparison valsartan 0.25 mg/kg versus valsartan 4 mg/kg under the alternative hypothesis that the treatment difference is 6 mmHg at a two-sided significance level of 0.05. Assuming 10% drop-out rate, the total targeted sample size to be randomized is 130 patients.
Key words	Randomized, multicenter, double-blind, double-dummy study, evaluate, dose response of valsartan on blood pressure reduction in children 1-5 years old (males/females) with hypertension, with or without chronic kidney disease

[redacted]

1 Introduction

1.1 Background

Hypertension in children is defined as a persistent systolic blood pressure (SBP) or diastolic blood pressure (DBP) ≥ 95th percentile for age, gender, and height (National High Blood Pressure Education Program 2004, Lurbe 2009). Obesity, insulin resistance, inactivity, ethnic predisposition to essential hypertension, and family history of hypertension are the common causes of hypertension in older children and adolescents. However, in children younger than 10 years of age, secondary causes of hypertension, including renal and reno-vascular disease, are more commonly observed (National High Blood Pressure Education Program 2004). Current epidemiologic data indicate that the prevalence of persistent hypertension in school-age children or above is approximately 1-2 percent, and in younger age children (< 6 years old) is extremely low (0.017%) (Morgenstern 1994, Reid and Chantler 2002). Most children found to be hypertensive in the < 6 year old age group present with severe, symptomatic hypertension due to underlying diseases (secondary hypertension). These patients often require pharmacological therapy to control blood pressure (Arar et al, 1994, Sadowski and Falkner 1996, Reid and Chantler 2002). There is a paucity of data regarding the efficacy and pharmacokinetics of antihypertensive medications in children. Antihypertensive medications have been extensively studied in adults, and most of them have been used commonly in hypertensive children, though few of them had been studied systematically in children until recently (Swindford and Portman 2004, Sinaiko 1994). As in adults, and based on a survey from North American pediatric nephrologists, ACE inhibitors and ARBs are commonly prescribed antihypertensive agents for children with hypertension and children with chronic kidney disease (Woroniecki and Flynn 2005).

Valsartan (Diovan®) is an angiotensin II receptor blocker (ARB), approved in adults for the treatment of hypertension. Valsartan 80-160 mg has been approved in the United States for use in adults since 1996. In the United States and other countries, valsartan 320 mg has been available for use in adults since 2001. Valsartan has been marketed in Europe in adults in doses of 80-160 mg since 1996 and in the highest dose of 320 mg since 2006. Valsartan has been approved for the treatment of hypertension in children 6-17 years of age in the United States since 2007 and in children 6-18 years of age in Europe since 2010.

Valsartan exerts its antihypertensive effect mainly by blocking the vasoconstriction, aldosterone secretion and sodium retention mediated by angiotensin II via selectively blocking the binding of angiotensin II to the AT1 receptor in tissues such as vascular smooth muscle and the adrenal gland. Valsartan has been shown to be effective in reducing both systolic and diastolic blood pressure in adults when used as monotherapy or in combination with other antihypertensive agents and is relatively well-tolerated.

The efficacy and safety of valsartan in children has been evaluated in four well controlled, prospective, multicenter studies where more than 700 hypertensive children aged 1-17 years old have been enrolled worldwide (Flynn 2008; Schaefer 2011; Schaefer 2011; Wells 2011; and Novartis, unpublished data). A wide dose range of valsartan (0.10 mg/kg to 4.94 mg/kg) has been evaluated in these studies. In studies in older children, valsartan was found to be efficacious, provided dose dependent reductions in blood pressure, and demonstrated

comparable efficacy to enalapril. Valsartan was well tolerated with a safety profile in older children not different from that observed in adults.

The efficacy of valsartan in younger children could not be consistently established. Inconsistent results were observed in two placebo-controlled trials: Study CVAL489A2307 in patients aged 1-5 years old and Study CVAL489K2303 in patients aged 6 months -5 years old. In Study CVAL489A2307, valsartan was efficacious compared to placebo during the placebo withdrawal period; however, a dose response was not demonstrated. In the other study, Study CVAL489K2303, although a trend in dose response was observed; no significant treatment difference compared to placebo was demonstrated.

Additional detailed summaries of these valsartan pediatric studies can be found in the investigator's brochure. The current study is designed to provide additional clinical data to determine the benefit/risk profile in children 1-5 years old.

1.2 Purpose

This study is part of the European Diovan® pediatric program and is conducted at the request of the EMA/Pediatric Committee (PDCO). Two previous trials, using valsartan, have been conducted in hypertensive children between 6 months and 5 years with mixed results. The EMA Committee for Medicinal Products for Human Use (CHMP) emphasized that a clinical need in this age group exists and that it would be relevant to conduct a new study (Section 3.2). The purpose of this study is to establish a dose response for valsartan solution in children 1-5 years old with hypertension (mean systolic blood pressure $\geq 95^{th}$ percentile), with or without chronic kidney disease (CKD). A sub-analysis will be performed to study the safety and tolerability of valsartan in children with CKD. An open-label phase has been added to study the safety of valsartan. The effects of valsartan on renal function and proteinuria will also be evaluated in CKD patients.

2 Study objectives

2.1 Primary objectives

To evaluate if a dose dependent reduction in mean systolic blood pressure (MSBP) exists when comparing two doses of valsartan solution (0.25 mg/kg and 4 mg/kg) over a 6 week period in children 1-5 years old with hypertension (MSBP $\geq 95^{th}$ percentile for age, gender and height), with or without CKD.

2.2 Secondary objectives

- To assess the efficacy of valsartan in reducing the mean diastolic blood pressure (MDBP) in children with hypertension.
- To assess the efficacy of valsartan in controlling the MSBP and MDBP in children with hypertension. The target mean BP is $<90^{th}$ percentile for age, gender and height.
- To assess the safety and tolerability profile of valsartan in children with hypertension, with or without CKD.
- To assess the effect of valsartan on proteinuria and eGFR in a subset of children with hypertension and CKD.

[redacted]

2.3 Exploratory objectives

None

3 Investigational plan

3.1 Study design

This is a 6 week, randomized, multicenter, double-blind, double-dummy study to evaluate the dose response of valsartan solution on blood pressure reduction in children 1-5 years old with hypertension, with or without chronic kidney disease, followed by a 20 week open-label phase with an optional titration period. Figure 3-1 shows the overall study design.

Period 1 is a 6 week double-blind dose ranging period to ensure that the maximum antihypertensive effect of valsartan will be reached. Period 2 is an open-label optional titration phase, where the safety of valsartan can be assessed including potential effects on proteinuria.

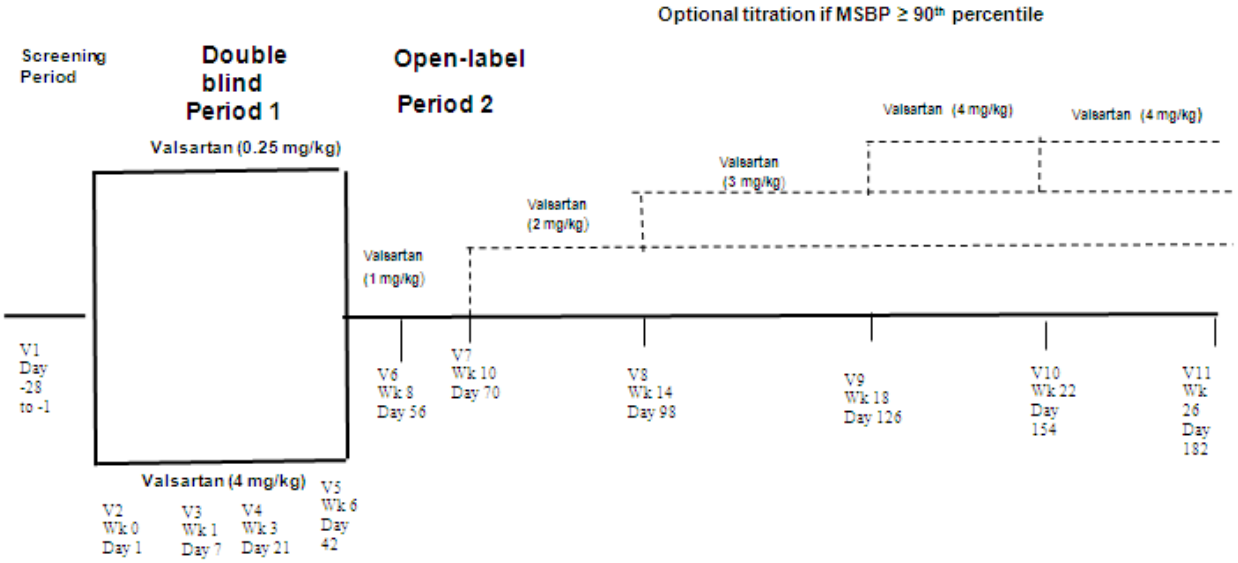
Patients entering the study receiving background antihypertensive treatments may continue on these medications as long as they meet the eligibility criteria for MSBP ($\geq 95^{th}$ percentile). The background therapy and dose should remain unchanged for the duration of the study. No patients will be permitted in the study with background RAAS blocker therapy (ARBs, ACEi, DRIs).

This study consists of three periods:

- A Screening period of up to 28 days
- Period 1: A six-week randomized, double-blind, double-dummy dose-ranging period consisting of 2 valsartan dose groups (0.25 mg/kg and 4 mg/kg), and randomization will be 1:1.
- Period 2: A 20 week open-label titration phase where all patients will start with 1 mg/kg valsartan for four weeks then be optionally titrated every four weeks. Patients may receive up to 4 mg/kg of valsartan.

[redacted]

Figure 3-1 Study design



Screening

A screening visit (Visit 1) will be performed 1 to 28 days before enrollment to test eligibility for study participation. A parent/guardian of the patient will sign the Informed Consent Form after the purpose and nature of the study has been clearly explained to them.

Washout period

Under the supervision of the study investigator, a wash-out period of 28 days will be included for eligible patients on prior treatments that inhibit the renin angiotensin aldosterone system (RAAS blockers), which include angiotensin receptor blockers (ARB), angiotensin converting enzyme inhibitors (ACEi) and direct renin inhibitors (DRI). During the wash-out period patients should come to the clinic approximately once a week for safety blood pressure measurements. If MSBP rises more than 20% above the 95th percentile for age, gender and height during wash-out, or if the investigator deems hypertensive treatment necessary, then the patient may commence with the study drug treatment earlier, once all eligibility criteria have been met.

Patients currently taking antihypertensive medications other than RAAS blockers, who have a MSBP $<95^{th}$ percentile for age, gender and height at screening, can be tapered off these medications according to investigator instruction and manufacturer's labeling, in order to meet entry criteria. Patients who are **not** on RAAS inhibitor therapy can enter the treatment phase of the trial (Visit 2) once the patient has achieved a MSBP $\geq 95^{th}$ percentile for age, gender and height, screening laboratory results have been received and reviewed, and all other inclusion criteria have been met. Patients currently taking non-RAAS blockers, who have a MSBP $\geq 95^{th}$ percentile for age, gender and height, can continue taking these antihypertensive medications throughout the trial provided their dose remains unchanged.

Dose ranging period (Period 1):

[redacted]

Patients should be seen in the clinic on a weekly basis during screening, to determine if they meet the blood pressure criteria (MSBP $\geq$ 95th percentile) for randomization. Qualified patients will be randomized and all Visit 2 procedures completed. If the patient's blood pressure does not meet criteria, the patient can return to the research center once a week for a qualifying blood pressure evaluation for up to 28 days, beyond which they will be considered a screen failure.

Decisions regarding patient study enrollment MUST be made based on office blood pressure readings (mean SBP/mean DBP) using the office automatic blood pressure monitor and appropriately sized cuff (Figure 3-2 Blood pressure cuff size), provided by the Sponsor. Following the automatic blood pressure check, the patient's blood pressure must then be taken using the auscultatory method. The auscultatory blood pressure check must confirm that the patient does have MSBP $\geq$ 95th percentile.

At Visit 2 (week 0), eligible patients will be randomized into the study using the Interactive Response Technology (IRT) system. Patients will be randomized to one of two valsartan treatment arms: valsartan 0.25 mg/kg or valsartan 4 mg/kg in a 1:1 ratio. Patients will remain on their dose for 6 weeks.

Open-label period (Period 2)

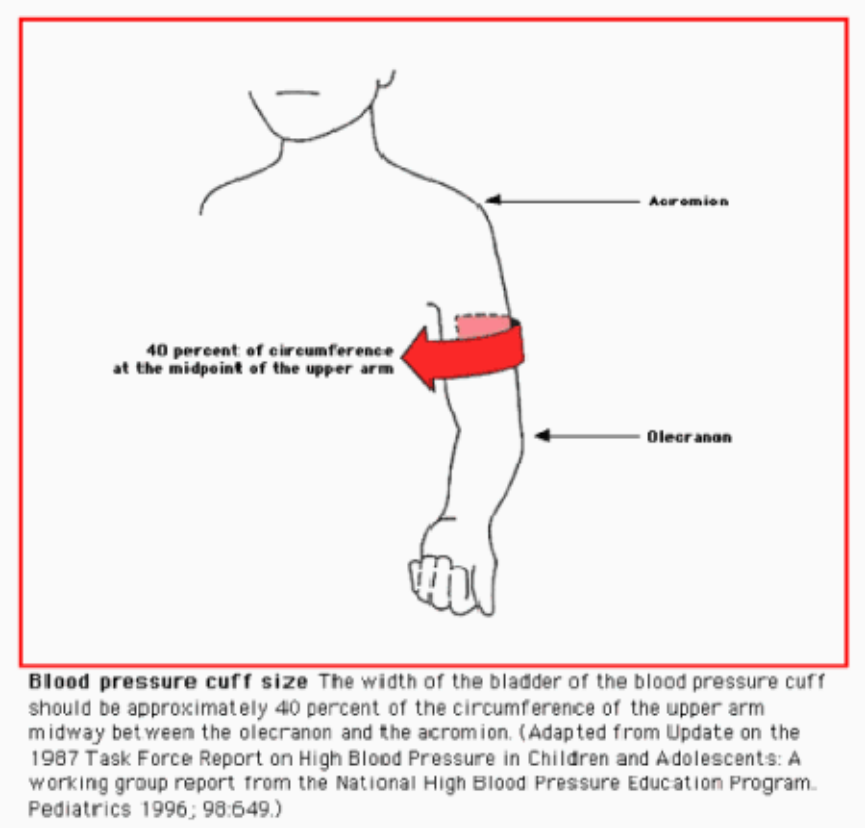
Following the double-blind treatment phase, all patients will move into a 20 week open-label phase (Visit 5). All patients will start on 1 mg/kg of valsartan and remain on this dose for 4 weeks. If, after 4 weeks (Visit 7) the patient's MSBP is $\geq$ 90th percentile for age, gender and height, the investigator may increase the dose to 2 mg/kg. If, after 4 weeks (Visit 8) the patient's MSBP is $\geq$ 90th percentile for age, gender and height, the investigator may increase the dose to 3 mg/kg. The dose can be further increased to 4 mg/kg at Visit 9, in order to control MSBP (<90th percentile). Patients can remain on the 4mg/kg dose from Visit 9 through the end of the study. The study medication may be down titrated at the investigator's discretion. After down titration the investigator may up titrate again to the maximum dose as necessary. The maximum dose the patient can take is 4 mg/kg for a maximum of 8 weeks.

Unscheduled visits can be performed as needed to monitor patient safety.

If, at any time after Visit 2, the patient's office-measured MSBP is $\geq$ 25% above the 95th percentile for age, gender, and height, the patient should be discontinued (Appendix 2).

[redacted]

Figure 3-2 Blood pressure cuff size



Blood pressure cuff size The width of the bladder of the blood pressure cuff should be approximately 40 percent of the circumference of the upper arm midway between the olecranon and the acromion. (Adapted from Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: A working group report from the National High Blood Pressure Education Program. Pediatrics 1996; 98:649.)

3.2 Rationale of study design

Two previous valsartan trials in hypertensive children between 6 months and 5 years showed mixed results with one study demonstrating a trend toward a positive dose response and the other not. Following consultation between the PDCO and the EMA committee CHMP, the CHMP indicated that the reasons behind the inconsistent results in the younger age group were not entirely understood and that no clear approach exists in the design of clinical trials for antihypertensive agents in the pediatric population. The CHMP recognized the clinical need in this age group and that it would be relevant to conduct a new study. The CHMP's Scientific Advice Procedure with the involvement of the PDCO was initiated for protocol assistance ([redacted]). Ultimately, an overall study design agreement was reached to perform an additional study in 1 to 5 year old children with hypertension using a similar design as in a previous study ([redacted]).

The study would consist of three periods. The first would be the Screening period, followed by a six-week randomized (1:1 ratio), double-blind, double-dummy dose-ranging period consisting of 2 valsartan dose groups (0.25 mg/kg and 4 mg/kg). The study would conclude with a 20 week open-label titration phase. All patients will be placed on a stabilized dose after the double-blind period (valsartan 1 mg/kg), with 3 optional titration steps during the open-label phase. The intent is to investigate the interrelation between the required starting dose

[redacted]

and potential risk factors. Duration of 26 weeks was selected as it is considered to provide the most appropriate time course to study proteinuria.

3.3 Rationale of dose/regimen, duration of treatment

There is currently no approved valsartan dose in this age group. The dose ranges to be used in this study have been tested in previous trials in hypertensive children between 6 months and 5 years.

An oral solution (3 mg/ml) will be used in the study. The mean valsartan concentration-time profiles following the oral administration of valsartan oral solution formulation and valsartan tablet formulation from previous pharmacokinetic studies showed the relative bioavailability of valsartan oral solution is 1.75 fold higher as compared to valsartan tablet formulation. In addition, the Cmax is 2.2 fold higher. Therefore, relatively higher exposure will be achieved in this study using the solution compared to the administration of tablets in adults.

It was also decided to extend the duration of this study to assess the safety of valsartan in children with hypertension, who also have chronic kidney disease.

3.4 Rationale for choice of comparator

Not applicable

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable

3.6 Risks and benefits

As seen in previous pediatric trials using valsartan, the beneficial effects of valsartan in reducing blood pressure in children were confirmed both with short-term and long-term administration. Additionally, valsartan was well tolerated.

The VAL489K2306 trial is being conducted at the request of the EMA/PDCO, in order to assess the safety, tolerability and efficacy in children 1-5 years of age with hypertension, with or without CKD.

There are several direct and perceived benefits for children participating in this trial. Some of the benefits can be summarized as the following:

- Participation in this study will allow patients to receive medical attention by pediatric hypertension experts during the entire study duration. During screening, a thorough physical examination, detailed medical history, and complete laboratory tests will be performed for each potential patient. Some medical conditions may be detected early and get attention sooner due to the increased medical attention participation in this study.
- Study participation will also provide an opportunity for parents of the patients to discuss their children's medical conditions with these experts in great detail and formalize an individualized treatment plan for hypertension. During study participation, the patient and parent will have access to physicians and their medical teams to address any questions or concerns. The risk to patients will also be further minimized by complying with the study protocol and close clinical monitoring

[redacted]

Some of the risks associated with this trial include:

- Hyperkalemia: Hyperkalemia is a known and identified risk with drugs that interfere with the renin-angiotensin system especially in patients with concomitant renal disease. Since at least 50% of patients enrolled in this trial will have CKD, it is likely that some will experience hyperkalemia. To ensure their safety, patients with a serum potassium level > 5.3 mmol/L during the trial will need to repeat the laboratory test (advisable within one week after results were sent). All patients with serum potassium > 5.3 mmol/L should be followed and appropriate medical care given. If the repeat value confirms serum potassium > 5.5 mmol/L, the patient must be immediately discontinued from the study and the appropriate medical care given.
- Study drug solution contains sucrose (0.3 g per milliliter) which should be taken into account in diabetic patients because it may increase blood sugar levels; methyl parahydroxybenzoate which may cause an allergic reaction (possibly delayed), and poloxamer (188) which may cause softened stools.
- Liver function monitoring:
  For patients with any clinically relevant degree of LFT elevation (AST/ALT/total bilirubin), frequent monitoring will be performed until the values approach either normal range or baseline values. For patients with LFT elevation of > 3 x ULN, a hepatitis panel test (A, B, C, D, E) will be requested and a retest will be done for the LFT and to rule out viral hepatitis. If the retest shows that the LFT elevation is still > 3 x ULN, then the patient must be discontinued from the study immediately. If the retest shows that the LFT elevation is less than or equal to 3 x ULN, the patient may remain in the study, if considered medically safe to do so by the investigator.
- Hypotension: Hypotension is an identified risk in certain patients and is an extension of the pharmacologic effect. Dizziness, vertigo, and syncope may be related to low blood pressure, but may also be associated with other conditions. The protocol has specific detailed procedures for careful blood pressure monitoring at each visit. The protocol has defined stopping rules for study medication or study discontinuation based on blood pressure measurements.
- As in any clinical study, there are always unknown risks and new side effects that are not now known could also occur.

The results from this trial will provide further information on the efficacy, safety, and tolerability of valsartan in hypertensive pediatric patients with or without CKD.

4 Population

The study population will consist of a representative group of 130, male and female children age 1-5 years by visit 2. All patients must have a history of hypertension defined as a MSBP $\geq$ 95th percentile to be eligible for randomization into this study. Approximately 50 sites are planned for this study. A total of 200 patients will be screened to randomize 130 patients with an anticipated screen failure rate of 35%. A drop out rate of 10% during the double-blind period is expected. A total of 116 patients are expected to complete the double-blind period and enter the open-label period. Patients will be stratified based on CKD status (yes /no).

[redacted]

At least 50% of patients enrolled will be CKD patients. CKD patients must have a documented history of CKD.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed. Parent(s)/guardian(s) have to provide consent in writing (written informed consent) after the purpose and nature of the study has been clearly explained to them.
2. Male or female, 1 to 5 years at baseline (visit 2), with a documented diagnosis of hypertension (National High Blood Pressure Education Program 2004)
3. CKD patients must be defined as any of the following criteria (Hogg et al 2003) (At least 50% of enrolled patients will be CKD-patients):
   a. Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by one or more of the following features:
      - Abnormalities in the composition of urine
      - Abnormalities in imaging tests
      - Abnormalities on kidney biopsy
   b. Estimated GFR <60 mL/min/1.73m2 (calculated by Modified Schwartz Formula) for ≥3 months, with or without the other signs of kidney damage described above.
4. MSBP (mean of 3 measurements) must be ≥95th percentile, and ≤25% above the 95th percentile, for age, gender and height, at baseline (visit 2) (Appendix 2), by office automatic blood pressure monitor and cuff, provided by the Sponsor. Confirmation of MSBP ≥95th percentile must be made using the auscultatory blood pressure method.
5. Able to swallow the valsartan solution
6. Body weight must be ≥8 kg and ≤40 kg at baseline
7. Must be able to safely washout prior ARB, ACEi and DRI therapy (if applicable) and other antihypertensive therapy (if applicable)

4.2 Exclusion criteria

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Any clinically significant physical abnormality or clinically relevant abnormal laboratory values (other than those relating to renal function) obtained at the screening visit (Visit 1), including the following:
   a. AST/SGOT or ALT/SGPT >3 times the upper limit of the reference range. Patients known to have active or chronic hepatitis will be excluded.
   b. Total bilirubin >2 times the upper limit of the reference range
   c. Estimated Glomerular Filtration Rate [eGFR] <30 mL/min/1.73m² (calculated using Modified Schwartz Formula)

[redacted]

   d. WBC count <3000/mm³
   e. Platelet count <100,000/mm³
   f. Serum potassium >5.3 mmol/L
   g. Hemoglobin <9 g/dL
2. Uncontrolled diabetes mellitus, as defined by the investigator
3. Unilateral, bilateral and graft renal artery stenosis
4. Current diagnosis of heart failure (NYHA Class II-IV)
5. Patients taking any of the following concomitant medications following screening:
   a. RAAS blockers other than study drug
   b. Lithium
   c. Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
   d. Non-steroidal anti-inflammatory drugs (NSAIDS), including selective COX-2 inhibitors, acetylsalicylic acid >3g/day, and non-selective NSAIDs (paracetamol/acetaminophen is permitted)
   e. Antidepressant drugs in the class of MAO inhibitors (e.g. phenelzine)
   f. Chronic use of stimulant therapy for ADD/ADHD
6. Patients who demonstrate clinically significant ECG abnormalities such as concurrent potentially life threatening arrhythmias or symptomatic arrhythmias are excluded, as are patients with second or third degree heart block without a pacemaker. Patients with ECG abnormalities associated with left ventricular hypertrophy are permitted to enroll.
7. Patients who have coarctation of the aorta with a gradient of ≥30 mmHg
8. Previous solid organ transplantation except renal transplantation. Renal transplant must have occurred at least 1 year prior to enrollment. Patient must be on stable doses of immunosuppressive therapy and deemed clinically stable by the investigator. Stable doses of immunosuppressive therapy are defined as no change in frequency or total daily doses of immunosuppressive therapy for at least two months prior to screening.
9. Patients known to be positive for the human immunodeficiency virus (HIV)
10. Any clinically significant medical condition that would put the patient at risk of experiencing an adverse event associated with the expected pharmacodynamic effects of the study drug
11. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of the study drug including, but not limited to, any of the following:
    a. History of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection.
    b. Currently active or previously active inflammatory bowel disease during the 12 months prior to Visit 1.
    c. Patients known to have currently active gastritis, duodenal or gastric ulcers, or gastrointestinal/rectal bleeding during the 3 months prior to Visit 1.

[redacted]

d. Patients known to have active pancreatic injury, pancreatitis or evidence of impaired pancreatic function/injury as indicated by abnormal lipase or amylase.
e. History of hepatic encephalopathy, a history of esophageal varices, or a history of porto-caval shunt.
f. Current obstruction of the urinary tract or difficulty in voiding due to mechanical or inflammatory conditions which is likely to require intervention during the course of the study or is regarded as clinically meaningful by the investigator.

12. Known or suspected contraindications to the study drug, including severe hepatic impairment, biliary cirrhosis, cholestasis and history of allergy to other ARBs or to ACEi(s) and/or DRIs
13. History of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin
14. Participation in any investigational drug study within 30 days prior to screening or within 5 elimination half-lives of the study drug prior to screening, or whichever is longer.
15. History of hypersensitivity to the study drug or to drugs of similar chemical classes
16. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency since the study drug solution contains sucrose.

If there is any question that the patient will not reliably comply, they should not be entered in the study.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

The sponsor will provide the following double-blind study medication (Day 1 – Day 42):

- VAL489 (Valsartan) 3 mg/ml oral solution
- Placebo to match VAL489 (Valsartan) 3 mg/ml oral solution

During the double-blind Period 1, a double-dummy design will be used since there will be volume differences between the doses.

The sponsor will provide the following open label study medication (Day 43 – Day 182):

- VAL489 (Valsartan) 3mg/ml oral solution

No other drugs will be supplied. Medication will be supplied in bottles. Sufficient medication will be provided for treatment according to the protocol.

Each study site will be supplied by Novartis with study drug. The study drug packaging has a 2-part label. A unique number is printed on each part of this label which corresponds to one of the 2 treatment arms. Investigator staff will identify the study drug bottle(s) to dispense to the patient by contacting the IRT system and obtaining the medication number(s). Immediately before dispensing the bottle(s) to the patient, investigator staff will detach the

[redacted]

outer part of the label from the packaging and affix it to the source document (drug label form) for that patient's unique patient number.

All bottles assigned by the IRT system will be recorded in the IRT database.

The drug labels will comply with local legal requirements and be printed in the local language.

Study drug must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated staff have access. Upon receipt, all study drugs should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will comply with the legal requirements of each country. They will contain no information about the patient but will carry the medication number.

Each patient will receive medication bottles at each visit. Patients will be instructed to take study medication once daily at approximately the same time each day, in the morning with or without food, except on the days of study visits. On the days of study visits the study drug should be taken after all study visit assessments have been completed.

5.1.2 Additional study treatment

No additional treatment beyond investigational treatment is requested for this trial.

5.2 Treatment arms

- Period 1:

VAL489 (Valsartan) 0.25 mg/kg or 4 mg/kg

VAL489 (Valsartan) 0.25 mg/kg or 4 mg/kg matching placebo

- Period 2:

VAL489 (Valsartan) 1 mg/kg, optional titration 2 mg/kg, 3 mg/kg and 4 mg/kg (max dose).

5.3 Treatment assignment, randomization

At Visit 2, all eligible patients will be randomized via Interactive Voice Response System to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates

the random assignment of medication numbers to study drug packs containing each of the study drugs.

The randomization scheme for patients will be reviewed and approved by a member of the IIS Randomization Group.

5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatments from the time of randomization up to Visit 5 (Week 6) using the following methods.

1. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study.
2. The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, and schedule of administration and appearance.

A double-dummy design is used because the identity of the study drugs cannot be disguised due to their different forms.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.10) and at the conclusion of the study.

An assessment will be done by the appropriate site personnel and the CTH for any patient whose treatment code has been broken inadvertently or for any non-emergency reason to assess whether or not study drug should be discontinued and, if applicable, whether the patient can continue into the next trial phase (e.g., open-label extension).

Starting from Visit 5 (Week 6) up to Visit 11 (Week 26) the identity of the treatments will be open-label.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient (parent) is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the Screening Log CRF.

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with study drug in packaging of identical appearance.

[redacted]

The investigational treatment packaging has a 2-part label. A unique randomization number is printed on each part of this label which corresponds to one of the "n" treatment arms and a specific visit. Investigator staff will identify the investigational treatment package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

Investigational treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all investigational treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the investigational treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial. Patients will be asked to return all unused investigational treatment and packaging at the end of the study or at the time of discontinuation of investigational treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational treatment, packaging, drug labels, and a copy of the completed drug accountability log to the CRO monitor or to the Novartis address provided in the investigator folder at each site.

5.5.4 Instructions for prescribing and taking study treatment

The investigator should insure that the patient's parent or guardian clearly understands the following dosing instructions:

Study drug will be dispensed at Visits 2, 3, 4, 5, 7, 8, 9 and 10. All study medication will be supplied in the form of an oral solution.

This study consists of two periods:

- Period 1: valsartan 0.25 mg/kg or 4 mg/kg and valsartan matching placebo 0.25 mg/kg or 4 mg/kg
- Period 2: valsartan 1 mg/kg open label, optional 2 mg/kg, 3 mg/kg and 4 mg/kg (max. dose).

Starting at Visit 7 (Week 10) valsartan will be optionally titrated from 1 mg/kg to 2 mg/kg. Valsartan will continue to be optionally up titrated in 1 mg/kg increments every 4 weeks (visits 8, 9 and 10) until maximum dose of 4 mg/kg is achieved. Titration criteria can be found in section 3.1.

[redacted]

Additionally, all dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

All kits of investigational treatment assigned by the IRT will be recorded/databased in the IRT.

The investigator should promote compliance by instructing the patient to take the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

First dose of study medication should be administered at Visit 2, after all study visit assessments have been completed. All study treatment will be taken orally and will be administered once daily, at approximately the same time each day, in the morning, with or without food, except on the days of study visits. On the days of study visits the study drug should be taken after all study visit assessments have been completed (see Section 6).

5.5.5 Permitted dose adjustments and interruptions of study treatment

The open-label study medication doses (Figure 3-1) may be down titrated, at the investigator's discretion. After down titration the investigator may up titrate again but cannot exceed the maximum dose of 4 mg/kg of valsartan.

Study drug treatment interruptions are only allowed for safety reasons.

All changes in study drug must be recorded on the Dosage Administration Record CRF.

5.5.6 Rescue medication

No rescue medication will be allowed.

Background antihypertensive medication other than RAAS blockers are allowed from screening through the end of study.

Use of background antihypertensive medication must be recorded on the Prior and concomitant anti-hypertensive medications CRF.

5.5.7 Concomitant treatment

All medications and significant non-drug therapies (including lifestyle intervention, physical therapy and blood transfusions) administered prior to the patient start of treatment with study drug must be listed on the Concomitant medications/Significant non-drug therapies prior to start of study CRF.

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the Concomitant medications/Significant non-drug therapies after start of study drug CRF.

All antihypertensive medication administered prior to the patient start of treatment with study drug, as well as antihypertensive medication continued or added must be listed on the Prior and concomitant anti-hypertensive medications CRF.

[redacted]

5.5.8 Prohibited treatment

Use of any of the treatments displayed in Table 5-1 is NOT allowed after screening until the end of the study. The prohibited medications and the specified timeframes are based on the potential that these medications may confound either the evaluation of efficacy or safety during the trial. Patients who are receiving such medication(s) should not be enrolled, or if ethically justified the medication(s) may be withdrawn prior to or at Visit 2.

Table 5-1 Prohibited treatment

Medication	Action to be taken
RAAS blockers other than study drug (e.g. ARB, ACEi, DRI, aldosterone antagonists)	Consult with Sponsor to determine if study discontinuation is required.
Lithium	Consult with Sponsor to determine if study discontinuation is required.
Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels	Consult with Sponsor to determine if study discontinuation is required.
Non-steroidal anti-inflammatory drugs (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid>3 g/day, and non-selective NSAIDs. Paracetamol/acetaminophen is permitted.	Discontinue study treatment if chronic use is needed. None, if acute use for less than 7 days. Consult with Sponsor to determine if study discontinuation is required if acute use is for 7 days or longer.
Steroid therapy: Chronic use of steroids is permitted as long as their use is stable at least 1 month prior to screening and does not increase during the study. Changes in steroid dose should not occur during double-blind phase. Decreases during the open-label phase are allowed.	Consult with Sponsor to determine if study discontinuation is required if steroid dose changed during the double-blind phase. Discontinue study treatment if dose increase in steroids is required for more than 7 days during open-label phase. No action if acute use for less than 7 days during open-label phase. Consult with Sponsor to determine if study discontinuation is required if acute use is for 7 days or longer.
Immunosuppressive therapy: Immunosuppressive therapy is permitted as long as their use is stable at least 2 months prior to screening. Dose increases due to weight change in order to keep patient within therapeutic range are permitted. Dose increases for other reasons (e.g., transplant rejection) are not permitted.	Discontinue if dose increase in immunosuppressive therapy was due to reasons other than weight change (e.g. transplant rejection).
Antidepressant drugs in the class of MAO inhibitors (e.g. phenelzine)	Consult with Sponsor to determine if study discontinuation is required.
Over The Counter decongestants are disallowed 24 hours prior to a scheduled study visit, after Visit 1	None
Chronic use of stimulant therapy for ADD/ADHD	Consult with Sponsor to determine if study discontinuation is required.

5.5.9 Discontinuation of study treatment and premature patient withdrawal

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for a visit or become lost to follow up for any other reason.

If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Completion CRF.

[redacted]

The investigator should discontinue study treatment for a given patient or withdraw the patient from the study if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Study drug must be discontinued for a given patient if the investigator determines that continuing it would result in a significant safety risk for that patient. If one of the following applies, the patient should be thoroughly evaluated by the Investigator within 48 hours, and should be discontinued from study drug.

- Withdrawal of informed consent
- MSBP is >25% above the 95th percentile for age, gender and height at any time during the study after baseline
- Symptomatic hypotension and MSBP ≤50th percentile for gender, age and height at any time during the study
- Any of the following laboratory abnormalities:
  - If patient has an eGFR <30 mL/min/1.73m^2, the patient will need a repeat lab test, advisable within one week after results were sent. If the repeat value confirms eGFR <30 mL/min/1.73m^2, the patient must be discontinued per valsartan label
  - >50 % decrease in eGFR from baseline
  - Severe anemia: defined as hemoglobin <9 g/dL
  - WBC <3000/mm3
- Hyperkalemia: If a serum potassium level is >5.3 mmol/L (as per central lab), the patient will need a repeat lab test, advisable within one week after results were sent. All patients with serum potassium of 5.3 mmol/L or higher should be followed and appropriate medical care given.
  If the repeat value confirms serum potassium > 5.5 mmol/L (as per central lab), the patient must be immediately discontinued from the study and the appropriate medical care given.
- Liver function monitoring:
  For patients with any clinically relevant degree of LFT elevation (AST/ALT/total bilirubin), frequent monitoring will be performed until the values approach either normal range or baseline values. For patients with LFT elevation of > 3 x ULN, a hepatitis panel test (A, B, C, D, E) will be requested and a retest will be done for the LFT and to rule out viral hepatitis. If the retest shows that the LFT elevation is still > 3 x ULN, then the patient must be discontinued from the study immediately. If the retest shows that the LFT elevation is less than or equal to 3 x ULN, the patient may remain in the study, if considered medically safe to do so by the investigator.
- Interruption of study drug treatment for longer than two consecutive weeks because of non-compliance.
- Any other protocol deviation that results in a significant risk to the patient's safety.

If one of the following applies, the patient should be thoroughly evaluated by the Investigator within 48 hours, and the investigator should consider discontinuation from study drug and contact the Sponsor if applicable:

[redacted]

- Patients with MSBP >20% above the 95th percentile for age, gender and height after visit 5 should be thoroughly evaluated by the Investigator to determine if the patient should continue on current therapy.
- Acute dehydration:
  If a patient presents with acute dehydration the patient's study drug is to be temporarily interrupted until the patient is fully hydrated for at least 3 days.

The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Completion CRF. Patients who discontinue study treatment before completing the study, and those who prematurely withdraw from the study for any reason, should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At a minimum, those patients will be contacted for safety evaluations during the 30 days following the last dose of study drug, including a final contact at the 30-day point.

Patients who discontinue study treatment should NOT be considered withdrawn from the study. A Study Drug Discontinuation form should be completed, giving the date and primary reason for stopping study treatment. See Section 6 for the required assessments of these patients after discontinuation of study treatment.

The investigator must also contact the IRT system to register the patient's discontinuation from study drug.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

Patients who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled patients.

5.5.10 Emergency breaking of treatment assignment

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Clinical Trial Head (CTH) that the code has been broken.

[redacted]

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT code break cards in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number, study drug name if available, patient number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable.

5.5.11 Study completion and post-study treatment

Study completion for a patient in this study is defined as having performed the final study visit within the time window of Visit 11.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

5.5.12 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as described in Section 6 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

6 Visit schedule and assessments

Screening/washout: The vital signs and medical history collected during the screening visit will be documented in source documents. Once the patient qualifies for the study (Visit 2), information from Visit 1 should be entered into the Visit 1 CRF.

Further details about the screening, washout and treatment period can be found in Section 3.1.

Table 6-1 lists all of the assessments and indicates with an "x" the visits when these assessments are performed. During the treatment period patients should be seen for all visits on the designated day with a visit window of ±7 days between visits 2 through 11.

All visits should be conducted at the same time of the day, in the morning, and approximately 24 hours (± 4 hours) post study drug dosage. Patients will be instructed not to take their study drug on the day of the visit before they have completed all study assessments for the same visit. If study drug has been taken on the day of the scheduled visit prior to assessments, the visit should be postponed and rescheduled within 3 days.

Unscheduled visits may be performed as needed at the discretion of the investigator to monitor patient's safety.All inclusion criteria are based upon office BP reading using the automated device provided by the Sponsor.

All data obtained from the assessments in Table 6-1 and all BP and AE data obtained from unscheduled visits must be supported in the patient's source documentation and will be added to the database accordingly.

[redacted]

Patients, who discontinue study treatment before completing the study, and those who prematurely withdraw from the study for any reason, should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. The site must register the patient discontinuation in the IRT system.

[redacted]

Table 6-1 Assessment schedule

Visit	1[1]	2	3	4	5	6	7	8	9	10	11/ End of study[6]
Day	-28 - -1	1	7	21	42	56	70	98	126	154	182
Week	-4 - -1	BL	1	3	6	8	10	14	18	22	26
Obtain informed consent	S										
Inclusion/exclusion criteria	S	S									
Medical history[2]	X	X[2]									
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Physical examination – complete	S				S						S
Physical examination – short		S	S	S			S	S	S	S	
Blood pressure [7]and pulse	X	X	X	X	X	X	X	X	X	X	X
Head Circumference	X	X			X			X			X
Height	X	X			X			X			X
Weight	X	X	X	X	X	X	X	X	X	X	X
ECG	X				X						X
Hematology	X	X			X			X	X	X	X
Complete blood chemistry	X	X			X			X			X
Abbreviated blood chemistry									X	X	
Urine dipstick	X	X			X						X
UACR/Cys. C GFR (in CKD only)[3, 4]		X			X					X	X
eGFR	X	X			X			X	X	X	X
IRT[5]	X	X	X	X	X		X	X	X	X	X
Washout prior RAAS treatments	X										
Dispense study drug		X	X	X	X		X	X	X	X	
Drug accountability			X	X	X		X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X

X = assessment to be recorded on clinical data base
S = assessment to be recorded on source documentation

[1]All patients have up to 28 days to meet MSBP enrollment criteria. Patients not taking RAAS blockers can qualify once the patient has achieved a MSBP ≥ 95th percentile for age, gender and height (Appendix 2), screening laboratory results have been received and reviewed, and all other inclusion criteria have been met (Section 3.1).
[2] Medical history is collected at Visits 1-2. If patient has any event after first dose of study medication, event is recorded as AE (Section 7).
[3] CKD is defined in Section 4.
[4]Urine collection will begin 3 days prior to the study visit. UACR and Cystatin C GFR tests are done in CKD patients only.
[5]IRT: Visit 1: Patient registration information entered at Visit 1, including body weight and CKD status; Visit 2: weight and CKD status entered into IRT and study drug assigned; Visit 5-weight

[redacted]

Visit	1[1]	2	3	4	5	6	7	8	9	10	11/ End of study[6]
Day	-28 - -1	1	7	21	42	56	70	98	126	154	182
Week	-4 - -1	BL	1	3	6	8	10	14	18	22	26

entered in IRT for open-label dose; Visit 8: weight entered in IRT for open-label dose
[6] End of study assessments must be done for patients who discontinue from the study any time after Visit 2.
[7] Blood pressure: 3 oscillometric readings are taken at every visit, followed by one auscultatory blood pressure measurement. At Visit 2, the auscultatory measurement must confirm that the patient does have hypertension (MSBP ≥ 95th percentile for age, gender and height).

6.1 Information to be collected on screening failures

If the patient fails to be enrolled into the treatment phase for any reason, the IRT system must be notified that the patient was a screen failure and the reason for not being enrolled will be entered on the screening log. Detailed instructions regarding use of the IRT will be provided in the IRT user manual.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include date of birth, sex, race and ethnicity, height, weight, and head circumference.

Relevant medical history/current medical condition data includes data until the start of study drug. Where possible, diagnoses, and not symptoms will be recorded. Patients with CKD as defined in Section 4 should have a corresponding medical history of chronic kidney disease etiology recorded.

Visit 1

At Visit 1, the investigator or investigator's staff will call into IRT and register the patient. During this call, the patient's date of birth, gender, CKD status, and body weight will be entered into the IRT, along with the patient number.

Visit 2

The patient is enrolled into the trial at Visit 2 once all eligibility criteria are met (within 28 days of Visit 1). At this visit, the investigator or investigator's staff will call into IRT and enter the patient's body weight and CKD status.

CKD status, age and region

At Visit 2, the investigator or staff will also enter the patient's CKD status (CKD or non-CKD patient). The CKD definition is discussed in Section 4. At least 50% of the patients enrolled into the trial must have CKD. IRT will be used to track CKD status at Visit 2. IRT will be used to prevent over enrollment of non-CKD patients, in order to ensure that a sufficient number of CKD patients are enrolled (e.g. should enrollment of 65 non-CKD patients be achieved, IRT will not permit enrollment and assignment of study drug to further non-CKD patients in the study). Patients will be stratified by CKD status.

[redacted]

Visit 2 to Visit 10

The IRT system will be called at every visit. Study medication number assignment will be at every dispensing visit (Visit 2-Visit 10). The dose of medication that the patient receives will be based on the patient's weight at Visit 2 for double blind, and at Visit 5 and Visit 8 during the open-label phase.

6.3 Treatment exposure and compliance

Study medication and concomitant therapies will be recorded on the Dosage Administration CRF, the Concomitant medication/significant therapies prior to study drug administration CRF, and the concomitant medications/significant non-drug therapies after study drug administration CRF.

Patient compliance with the study drug treatment will be assessed by the investigator and/or study personnel using pill count, information from the patient/caregiver and drug accountability. This information should be captured in the source documents and in the CRF. Patient compliance should be at least 75% during the study. The investigator and/or study personnel will counsel the patient on proper method of taking the study drug as appropriate to ensure compliance during the trial. Patients who miss study drug for 2 weeks consecutively or more should be discontinued.

6.4 Efficacy

The following efficacy assessments will be performed as scheduled in Table 6-1.

6.4.1 Office blood pressure

Patient's blood pressure should be measured in the same position at every visit (lying down, sitting, being held in parent's arms or lap, etc). Systolic and diastolic blood pressures will be measured three times at 2-3 minute intervals. The arithmetic mean of these three blood pressure measurements will be used as the mean office blood pressure (MSBP and MDBP) for that visit, and will be recorded in the CRF. All blood pressure measurements will be recorded in the patient's source documents. The pulse rate is a safety assessment and will be performed immediately after the 3 blood pressure measurements. Every effort should be made to minimize staff-patient interaction, such as talking, for maximum reproducibility.

Automated arterial blood pressure determinations will be made with an automatic blood pressure monitor and appropriate size pediatric/small cuff in accordance with the Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV (Williams et al, 2004). The automatic blood pressure monitor and cuff will be provided by the Sponsor. The automated blood pressure machine will be used at every visit. After all three blood pressures are taken for a patient, study staff should print out the three BP readings and place it in the patient's source document, noting the patient's initials, and corresponding visit date and time on the BP record. A photocopy of the BP readings should also be made, as the printer ink may fade over time. The oscillometric method is to be used at every visit.

One auscultatory blood pressure reading using a calibrated standard sphygmomanometer and appropriate cuff size must be taken, following the three oscillometric readings, at every visit.

[redacted]

The reading will be documented in the patient's source document and CRF. At Visit 2, patient hypertension must be confirmed (MSBP ≥95th percentile for age, gender and height) by the auscultatory blood pressure method.

Arterial blood pressure determinations will be made in accordance with the *National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents* (NHBPEP Fourth Report 2004). Tables to determine the percentile for age, gender and height are provided in Appendix 2.

With the arm supported at the level of the heart, systolic pressure will be recorded when the initial sound is heard (Phase I of the Korotkoff sound); diastolic pressure will be recorded at the disappearance of the sound (Phase V of the Korotkoff sound). The cuff should be deflated at a rate not greater than 2 mmHg/second. At the first study visit, the arm in which the highest systolic blood pressure is found will be the arm used for all subsequent readings throughout the study and should be documented in the source documents. Every effort will be made to have the same staff member obtain blood pressure measurements for the same patient, at the same time of day in the morning, using the same equipment, at each visit.

6.4.2 Appropriateness of efficacy assessments

The efficacy parameters selected are standard for this indication and patient population.

6.5 Safety

The safety assessments consist of (serious) adverse event monitoring and the following evaluations. The assessments will be performed as scheduled in Table 6-1. Clinically notable values are defined in Appendix 1.

6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular (including blood pressure, pulse rate and ECG) and neurological system.

A short physical examination will include the examination of vital signs, heart, lungs, abdomen, extremities and any other evaluation the Investigator considers appropriate based on the patient's clinical status at the time of the visit.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the start of study drug must be included in the patient's Relevant Medical History/Current Medical Conditions CRF. Significant findings made after the start of study drug must be reported as an Adverse Event.

6.5.2 Vital signs

Blood pressure measurements are efficacy assessments. The pulse rate will be measured for 30 seconds just after the last blood pressure measurement.

6.5.3 Height, weight, and head circumference

Height in centimeters (cm), body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes), and head circumference will be measured.

[redacted]

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected, except for urine dipstick. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. Unscheduled local lab CRFs will be available, should a local lab be used in an emergency. For UACR see Section 6.5.4.4.

Clinically notable laboratory findings are defined in Appendix 1.

6.5.4.1 Hematology

Hematology laboratory assessments are performed at Visits 1, 2, 5, 8, 9, 10 and 11.

- Hematology: red blood cell count, hemoglobin, hematocrit, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count

6.5.4.2 Clinical chemistry

Complete blood chemistry laboratory assessments are performed at Visits 1, 2, 5, 8 and 11.

- Complete blood chemistry: urea, creatinine, non-fasting glucose, total bilirubin, AST/SGOT, ALT/SGPT, ALP, sodium, potassium, bicarbonate (total CO_2), chloride, calcium, phosphorous, total protein, albumin, uric acid, cholesterol, triglycerides and eGFR

Abbreviated blood chemistry laboratory assessments are performed at Visits 9, and 10.

- Abbreviated blood chemistry: urea, creatinine, sodium, potassium, bicarbonate (total CO_2) and eGFR

Cystatin C is obtained only for CKD patients at Visits 2, 5, 10 and 11.

6.5.4.3 Urinalysis

Urine dipstick analyses will be done locally on site at Visits 1, 2, 5, and 11. Materials will be provided by the central laboratory.

- Urinalysis: pH, specific gravity, glucose, protein, bilirubin, ketones, leukocytes, blood

[redacted]

6.5.4.4 Urinary albumin creatinine ratio (UACR)

For CKD patients, UACR will be measured from 3 consecutive early morning urine collections, beginning 3 days prior to the scheduled visit (see Table 6-1). UACR will be measured at Visits 2, 5, 10, and 11.

Urine collection materials and instructions will be provided to the patients prior to their visit. The patients will collect these three samples on the three days prior to their study visit and they will bring them when they return to the site. A central laboratory will be used for analysis of UACR samples. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. UACR will be calculated as follows:

UACR [mg/mmol] = urine albumin [mg/L] / urine creatinine [mmol/L]

6.5.4.5 Estimated Glomerular filtration rate (eGFR)

Schwartz GFR

For all patients, eGFR will be calculated using the Modified Schwartz Formula (Schwartz et. al 1976). This formula to estimate eGFR uses serum creatinine, height and a constant depending on age and gender:

eGFR [ml/min/1.73m2] = k * Height [cm] / Serum Creatinine [mg/dL]

Age	K
< 1 year	**0.45**
1 to 12 years	**0.55**
13 to 20 years (adolescent females)	**0.55**
13 to 20 years (adolescent males)	**0.70**

(Schwartz et al 1976)

Cystatin C eGFR

For CKD patients, the eGFR will also be calculated using the cystatin C value.

A serum cystatin C sample will be collected and the GFR will be estimated with the following formula (Filler et al 2003):

Log GFR [ml/min/1.73m2] = 1.962 + [1.123 * log (1 / serum cystatin C)]

6.5.5 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed at Visits 1, 5, and 11. The tracings will be dated and signed by the physician who provides the clinical interpretation of the ECG. The patient's identification number, the date and actual time of the tracing, and the study code "Study CVAL489K2306" must appear on each ECG tracing. In the CRF any ECG abnormalities will be recorded.

[redacted]

6.5.6 Pregnancy and assessments of fertility

Not applicable

6.5.7 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

6.6 Other assessments

Parents of the patients will be given a taste assessment at the final study visit. Investigator staff will ask the parent to evaluate how their child interpreted the taste of the study medication throughout the trial. The study staff will document this information in the patient's source document and complete this on the End of Study Case Report Form.

6.6.1 Resource utilization

Not applicable

6.6.2 Health-related Quality of Life

Not applicable

6.6.3 Pharmacokinetics

Not applicable

6.6.4 Pharmacogenetics/pharmacogenomics

Not applicable.

6.6.5 Other biomarkers

Not applicable

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

[redacted]

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for labs and other test abnormalities are included in Appendix 1

.

Adverse events should be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them accompanied by the following information.

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities

All adverse events must be recorded on the Adverse Events CRF with the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the study drug (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. to action taken regarding study treatment
5. whether it constitutes a serious adverse event (SAE)
6. whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
7. its outcome (continuing/not continuing)

An SAE is defined as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

[redacted]

  - social reasons and respite care in the absence of any deterioration in the patient's general condition

- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

The investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents, however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later).must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

[redacted]

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship of any SAE to study treatment, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate; see to section 5.5.9
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded on appropriate CRF pages.

7.4 Pregnancy reporting

Not applicable

[redacted]

7.5 Prospective suicidality assessment

Not applicable

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff must enter the information required by the protocol onto the Novartis CRFs that are printed on 2-part, non-carbon-required paper. Field monitors will review the CRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. The CRFs are forwarded to a designated Contract Research Organization (CRO) working on behalf of Novartis by field monitors or by the investigational site, with one copy being retained at the investigational site. Once the CRFs are received by the CRO, their receipt is recorded, the original copy scanned into the database for processing, and then placed in Central Files.

8.3 Database management and quality control

Data from the CRFs are entered into the study database by Contract Research Organization (CRO) staff following their own internal standard operating procedures that have been reviewed and approved by Novartis.

[redacted]

Subsequently, the entered data are systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Errors or omissions are entered on Data Query Forms, which are returned to the investigational site for resolution. The signed original and resolved Data Query Forms are returned back to the CRO so the resolutions can be entered into the database and a copy is kept with the CRFs at the investigator site. Quality control audits of all key safety and efficacy data in the database are made prior to locking the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all IRT recorded dosage changes will be tracked using an Interactive Voice Response System (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to a designated CRO.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

8.4 Data Monitoring Committee

Not required

8.5 Adjudication Committee

Not required

9 Data analysis

9.1 Analysis sets

The following analysis populations will be defined for statistical analyses:

Randomized Set (RAN) - All patients who receive a randomization number, regardless of receiving double blind study medication.

Full-analysis Set (FAS) - All patients randomized with at least 1 follow-up efficacy assessment. Following the intent-to-treat principle, patients will be analyzed according to the treatment assigned at randomization. The primary analysis will be performed on the FAS population. However, patients who were not qualified for randomization and were inadvertently randomized into the study are excluded from the FAS, provided these patients did not receive study drug.

Per-protocol Set (PPS) - All patients in FAS without any major protocol deviations. This supplement efficacy population is used to assess robustness of the primary analysis results.

[redacted]

The major protocol deviations will be pre-specified prior to unblinding the treatment codes for analyses.

Safety Set (SAF) - All patients who received at least one dose of study medication. Patients will be analyzed according to treatment they received.

Open-label Full Analysis Set (OFAS) - All patients entering the open label period with at least one follow-up efficacy assessment during open label period.

Open-label Safety Set (OSAF) - All patients who received at least one dose of trial medication in open-label period.

9.2 Patient demographics and other baseline characteristics

Patient demographics and baseline characteristics will be summarized by treatment group for randomized patients. Continuous variables (e.g. age, weight, MSBP, MDBP) will be summarized with descriptive statistics (n, mean, standard deviation, median, minimum, maximum). Qualitative variables (e.g. age group, gender and race) will be summarized with counts and percentages. The summaries will be performed on Randomized Set (RAN).

Comparisons of treatment groups with respect to the demographics and baseline characteristics will be performed using chi-square tests or F tests as appropriate. The results of these tests are provided for descriptive purposes, and will not be used as a formal basis to determine the factors to be included in statistical models.

Relevant medical history and continued medical conditions will be summarized by treatment group for randomized patients.

9.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Duration of exposure to study drug will be summarized by treatment group with descriptive statistics for safety set (SAF) during double-blind period. Duration of exposure to study drug in open-label period will be summarized by dose with descriptive statistics for patients in the Open-label Safety Set.

Concomitant medications and significant non-drug therapies will be summarized with frequency tables for patients in safety set and open-label safety patients.

9.4 Analysis of the primary variable(s)

The primary objective is to evaluate if a dose dependent reduction in MSBP exists when comparing two doses of valsartan solution (0.25 mg/kg and 4 mg/kg) over a 6 week period in children 1-5 years old with hypertension (MSBP $\geq 95^{th}$ percentile for age, gender and height), with or without CKD. The primary statistical model to be used is an analysis of covariance (ANCOVA) model with treatment and CKD strata as factors, and baseline MSBP as a covariate.

9.4.1 Variable

The primary efficacy variable is change from baseline (Week 0) in mean systolic blood pressure (MSBP) at Week 6 endpoint. For each patient, the last post-baseline measurement

[redacted]

during the double-blind period will be carried forward to Week 6 endpoint measurement for the variable to be analyzed. The primary analysis timepoint will be the Week 6 endpoint. The primary analysis will be performed on the Full-analysis Set (FAS).

9.4.2 Statistical model, hypothesis, and method of analysis

The null hypothesis is that there is no treatment difference in the reduction of MSBP between dose groups 0.25mg/kg and 4 mg/kg. The alternative hypothesis is that there is a difference between dose groups 0.25 mg/kg and 4 mg/kg.

The comparison will be tested at a two-sided significance level of 0.05. The change from baseline in MSBP at Week 6 endpoint during double-blind period will be analyzed using an analysis of covariance model (ANCOVA) with treatment and CKD strata as factors and baseline MSBP as a covariate for the FAS population.

9.4.3 Handling of missing values/censoring/discontinuations

For patients with missing values at Week 6, the last post-baseline observation during double-blind will be carried forward (LOCF) as the Week 6 endpoint.

9.4.4 Supportive analyses

In addition to the primary analysis based on the FAS population, a similar analysis will also be performed on the PPS population as a supplementary assessment.

To further assess the dose response, an analysis of covariate (ANCOVA) will be performed on the change from baseline at Week 6 endpoint in MSBP with CKD strata as a factor, dose per body weight as the main regressor, and baseline MSBP as a covariate. The analysis will be performed for the FAS population. The least-squares mean estimate for the slope will be provided.

The change from baseline in MSBP during double-blind period will be summarized by treatment and study week for the FAS and PPS populations respectively.

9.5 Analysis of secondary variables

9.5.1 Key secondary variables

- Change from baseline in mean diastolic blood pressure (MDBP) at Week 6 and end of study.
- Percentage of patients achieving MSBP < 90^{th} percentile for age, gender and height at Week 6 endpoint and end of study.
- UACR response (defined as % change from baseline in UACR≤ 25%) at Week 6 endpoint and end of study.

9.5.2 Efficacy variables

To evaluate the overall blood pressure changes for patients treated with valsartan throughout the study, the change from baseline (Week 0) in MSBP at the end of study will be summarized by open-label visits for OFAS population. A similar summary will be provided for MDBP.

[redacted]

9.5.3 Safety variables

The assessment of safety will be based mainly on the frequency of adverse events and on the summary of laboratory values for the safety populations. Other safety data (e.g. weight, height, resting pulse and head circumference) will be summarized as appropriate. The safety (SAF) and open-label safety (OSAF) populations will be used as appropriate for summaries of the double-blind and open-label periods.

Adverse events newly occurring or worsening during the double-blind treatment period and open-label period will be summarized by primary system organ class, preferred term, and treatment (only for double-blind period). Suspected study-drug related adverse events will be summarized similarly.

Serious adverse events and adverse events leading to study drug discontinuation (based on CRF AE data) will be summarized by primary system organ class, preferred term, and treatment, and will be listed by patient.

Laboratory data will be summarized by treatment for change from baseline and for occurrence of abnormality as appropriate.

9.5.4 Resource utilization

Not applicable

9.5.5 Health-related Quality of Life

Not applicable

9.5.6 Pharmacokinetics

Not applicable

9.5.7 Pharmacogenetics/pharmacogenomics

Not applicable

9.5.8 Biomarkers

Not applicable

9.5.9 PK/PD

Not applicable

9.6 Interim analyses

Not applicable

9.7 Sample size calculation

The sample size of 116 completed patients is calculated based on the primary efficacy variable, change from baseline in mean systolic blood pressure, and a standard deviation of 11 mmHg (based on previous data) is used. The sample size is calculated to ensure at least 80% power to detect statistical significance for the comparison valsartan 0.25 mg/kg versus

valsartan 4 mg/kg under the alternative hypothesis that the treatment difference is 6 mmHg at a two-sided significance level of 0.05. Assuming 10% drop-out rate, the total targeted sample size to be randomized is 130 patients.

9.8 Power for analysis of key secondary variables

Not applicable

9.9 Interim analyses

There will be no interim analysis for this study.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

10.3 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all

[redacted]

of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

11 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as requests to approve deviations will not be granted.

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days.

[redacted]

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[redacted]

13 Appendix 1: Clinically notable laboratory values

Hematology

Erythrocyte count	>50% increase, >30% decrease
Hemoglobin	>50% increase, >30% decrease
Hematocrit	>50% increase, >30% decrease
Leukocyte count	>50% increase, >50% decrease
Platelet count	>75% increase, >50% decrease

Blood Chemistry

Albumin	>50% increase, >25% decrease
Urea	>50% increase
Creatinine	>50% increase
Glucose	>50% increase, >50% decrease
Total bilirubin	>100% increase
SGOT / AST	>150% increase
SGPT / ALT	>150% increase
Sodium	>5% decrease
Potassium	>20% increase, >20% decrease, or any value >5.3 mmol/L
Chloride	>10% increase, >10% decrease
Calcium	>10% increase, >10% decrease
Uric Acid	>50% increase
GFR (Schwartz)	>25% decrease

Clinically notable laboratory values will be forwarded to Novartis at the same time when the sites are notified by the Central Lab.

[redacted]

Appendix 2: Pediatric blood pressure tables and growth charts

Blood pressure percentiles will be determined with the below BP tables which were published by the *National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents* (NHBPEP Fourth Report 2004, Lurbe 2009).

Height percentiles will be determined with below growth charts published by *Centers for Chronic Disease Control and Prevention* (http://www.cdc.gov/growthcharts).

Using the tables

Use the correct gender growth chart to determine the height percentile.

Measure and record the child's MSBP and MDBP.

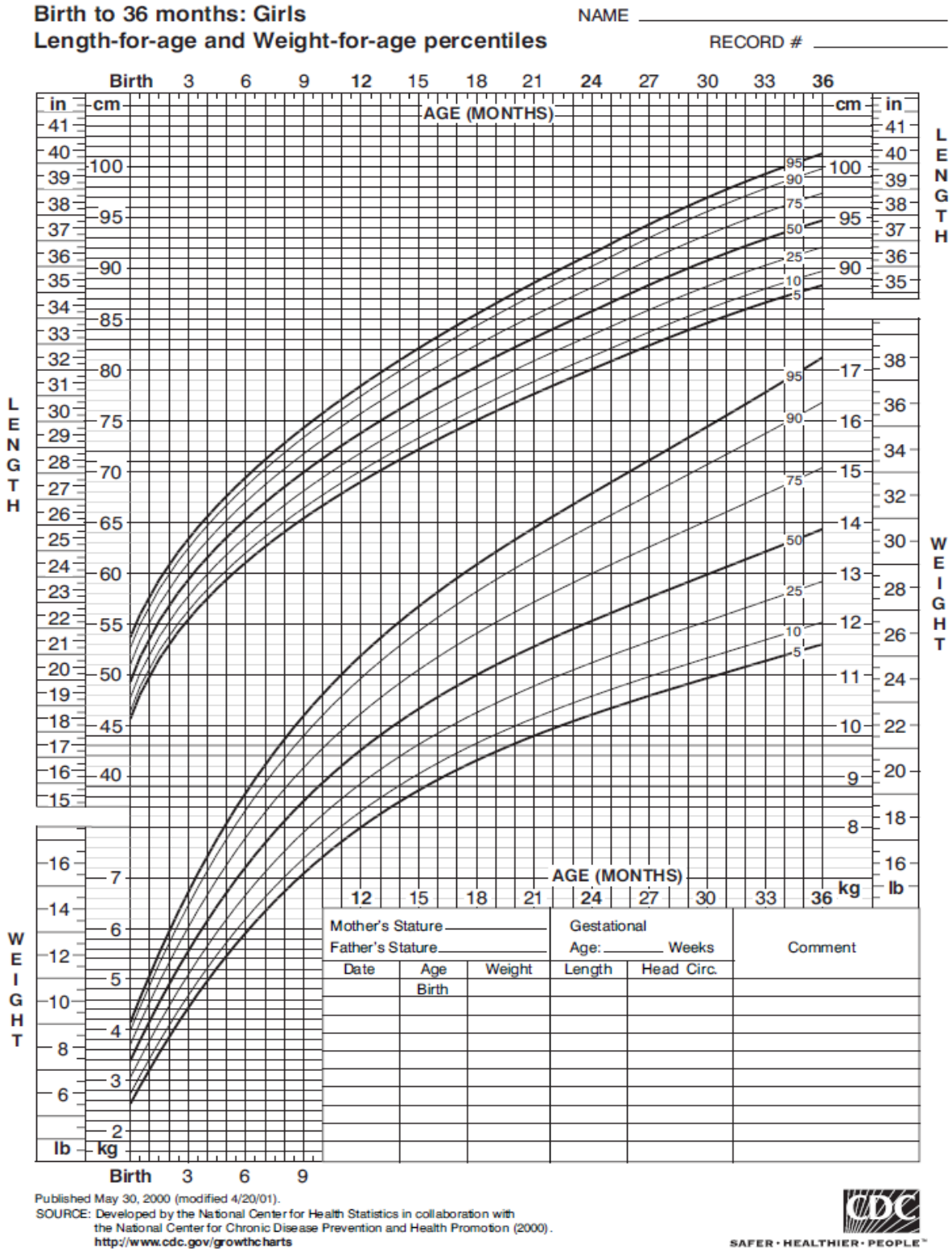
Use the correct gender table for SBP and DBP.

Find the child's age on the left side of the table. Follow the age row horizontally across the table to the intersection of the line for the height percentile (vertical column).

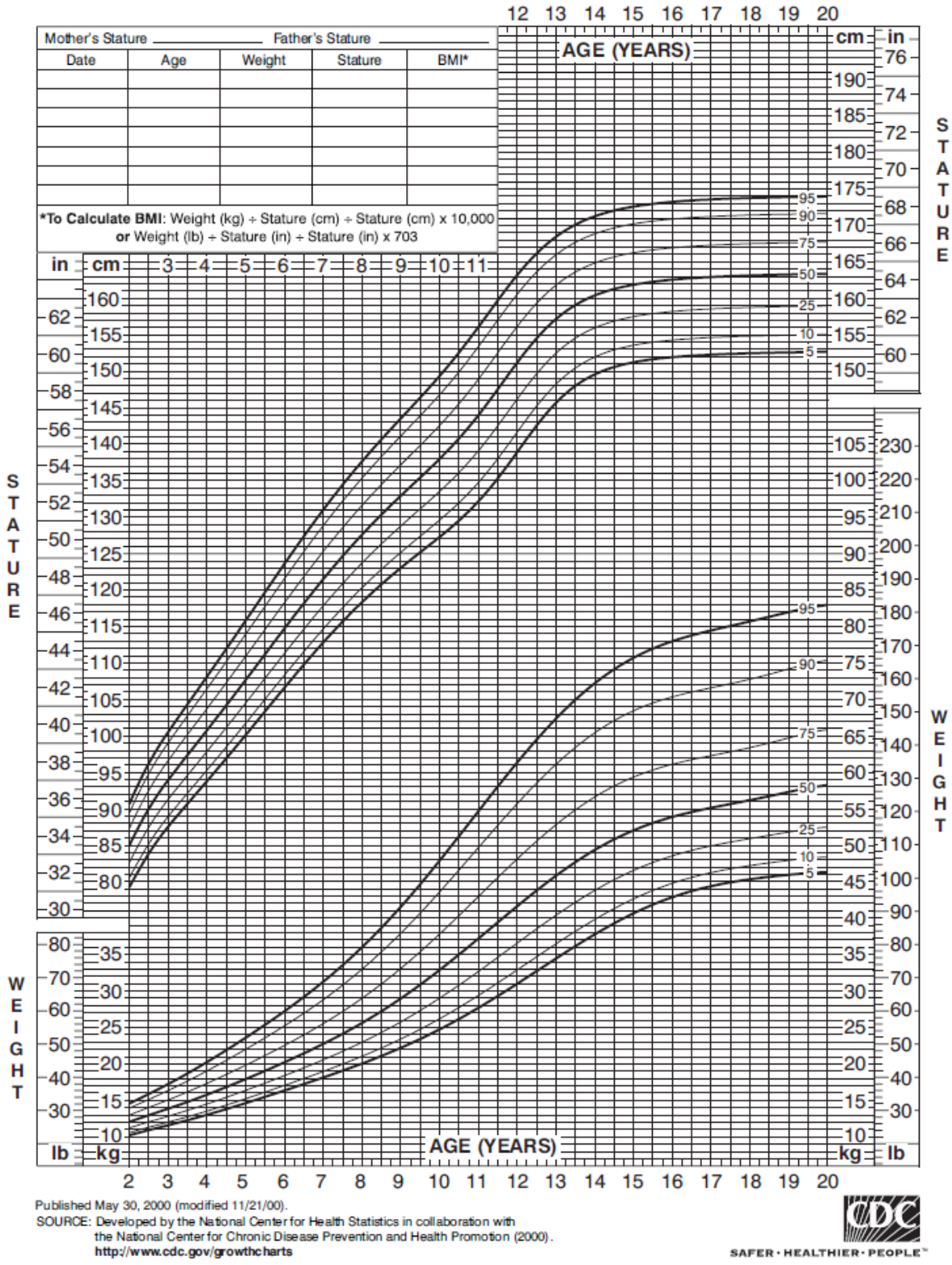
There, find the 50th and 95th percentiles or values for 20% and 25% above 95th percentile for SBP in the left columns and for DBP in the right columns.

[redacted]

Special methods and scales



[redacted]


2 to 20 years: Girls
Stature-for-age and Weight-for-age percentiles
NAME
RECORD #
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
AGE (YEARS)
STATURE
WEIGHT
95
90
75
50
25
10
5
Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts
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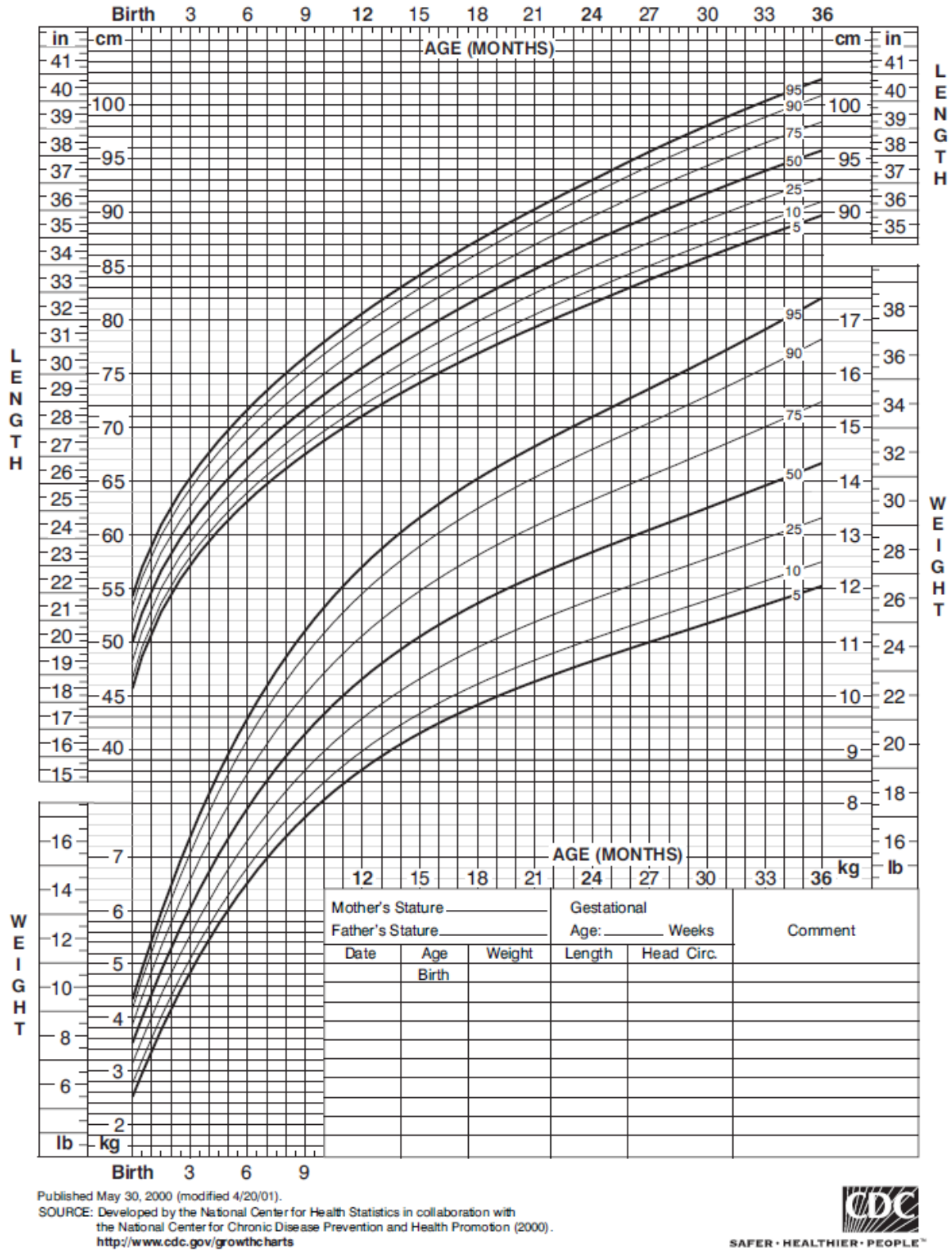
[redacted]



Published May 30, 2000 (modified 4/20/01).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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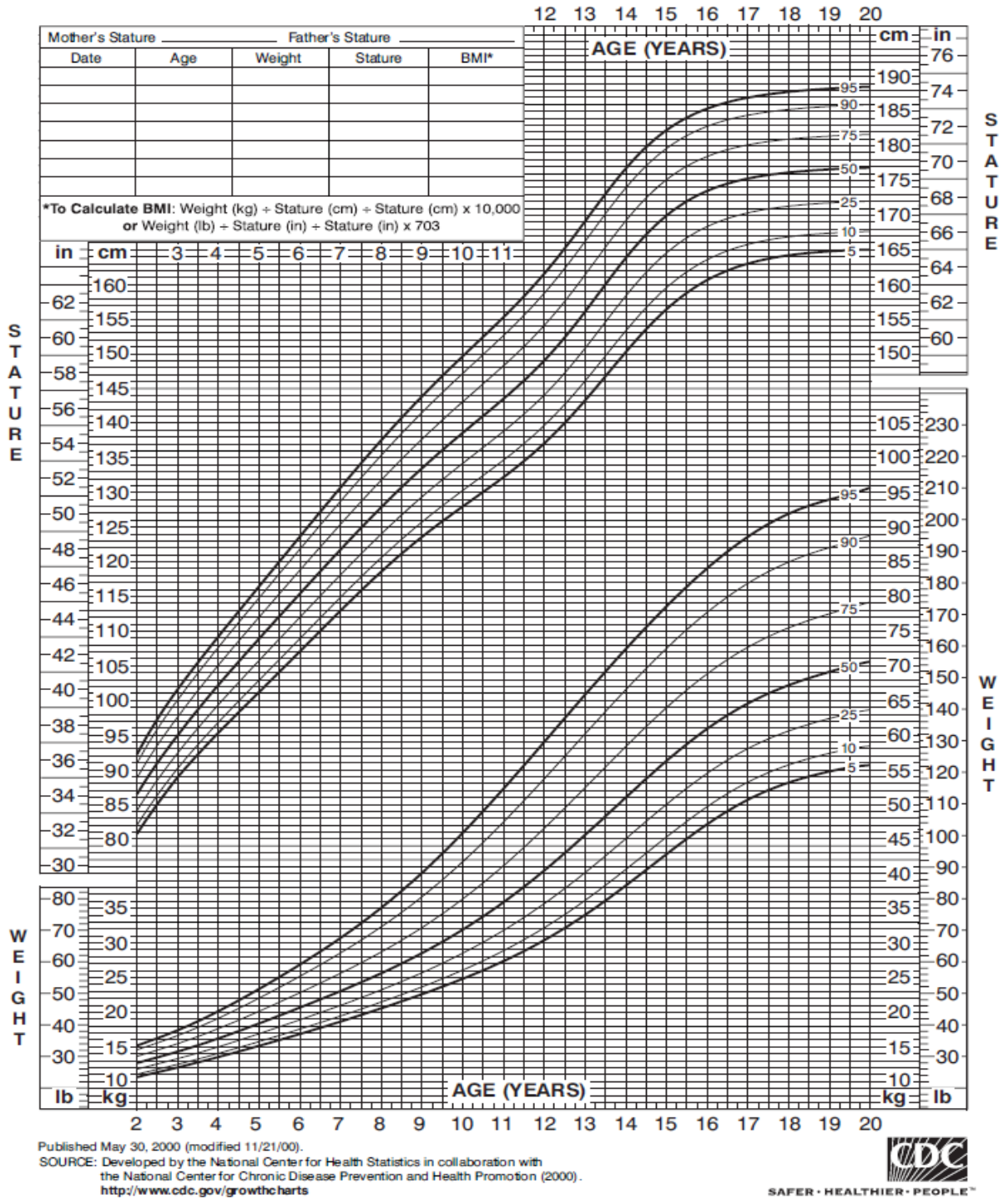
[redacted]


2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles
NAME
RECORD #
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
AGE (YEARS)
STATURE
WEIGHT
95
90
75
50
25
10
5
Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts
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[redacted]

BP Levels for girls by Age and Height Percentile (1-6 years old)

Age (years)	BP Percentile	SBP percentile of height (mmHg)							DBP percentile of height (mmHg)						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	20%	120	121	122	125	126	127	128	67	68	68	70	71	71	72
	25%	125	126	128	130	131	133	134	70	71	71	73	74	74	75
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	20%	122	124	125	126	128	130	131	73	74	74	76	77	78	78
	25%	128	129	130	131	134	135	136	76	78	78	79	80	81	81
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	20%	125	125	126	128	130	131	132	78	79	79	80	82	82	83
	25%	130	130	131	134	135	136	138	81	83	83	84	85	85	86
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	20%	126	127	128	130	132	133	134	82	82	83	84	85	85	86
	25%	131	133	134	135	138	139	140	85	85	86	88	89	89	90
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	20%	128	128	130	132	133	134	136	84	85	85	86	88	88	89
	25%	134	134	135	138	139	140	141	88	89	89	90	91	91	93
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	20%	130	131	132	133	136	137	138	86	86	88	89	89	90	91

[redacted]

Age (years)	BP Percentile	SBP percentile of height (mmHg)							DBP percentile of height (mmHg)						
	25%	135	136	138	139	141	143	144	90	90	91	93	93	94	95

Source: The Fourth Report on the Diagnosis. Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, Pediatrics. Vol. 114, pp. 555.
Table modified to delete 99th percentile values and to include calculated percentages (20% and 25 %) above 95th percentile values for ease of reference.

[redacted]

BP Levels for boys by Age and Height Percentile (1-6 years old)

Age (years)	BP Percentile	SBP percentile of height (mmHg)							DBP percentile of height (mmHg)						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	20%	118	119	121	124	125	127	127	65	65	66	67	68	70	70
	25%	123	124	126	129	130	133	133	68	68	69	70	71	73	73
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	20%	121	122	125	127	130	131	132	71	71	72	73	74	76	76
	25%	126	128	130	133	135	136	138	74	74	75	76	78	79	79
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	20%	125	126	128	131	132	134	136	76	76	77	78	79	80	80
	25%	130	131	134	136	138	140	141	79	79	80	81	83	84	84
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	20%	127	128	131	133	134	137	138	79	80	82	83	84	85	85
	25%	133	134	136	139	140	143	144	83	84	85	86	88	89	89
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	20%	130	131	132	134	137	138	139	83	84	85	86	88	89	89
	25%	135	136	138	140	143	144	145	86	88	89	90	91	93	93
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	20%	131	132	134	137	138	140	140	86	86	88	89	90	91	91

[redacted]

Age (years)	BP Percentile	SBP percentile of height (mmHg)							DBP percentile of height (mmHg)						
	25%	136	138	140	143	144	146	146	90	90	91	93	94	95	95

Source: The Fourth Report on the Diagnosis. Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, Pediatrics. Vol. 114, pp. 555.
Table modified to delete 99th percentile values and to include calculated percentages (20% and 25 %) above 95th percentile values for ease of reference.

[redacted]