Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Diovan / Angiosan / Valsartan Novartis (valsartan)

SE/W/0026/pdWS/001

Marketing Authorisation Holder: Novartis Sverige AB

Rapporteur:	SE
Finalisation procedure (day 120):	7 July 2017

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Diovan / Angiosan / Valsartan Novartis
INN (or common name) of the active substance(s):	valsartan
MAH:	Novartis Sverige AB
Currently approved Indication(s)	<u>Hypertension (only 40 mg)</u> Treatment of hypertension in children and adolescents 6 to 18 years of age. <u>Hypertension (only 80 mg, 160 mg and 320 mg)</u> Treatment of essential hypertension in adults, and hypertension in children and adolescents 6 to 18 years of age. <u>Recent myocardial infarction (only 40 mg, 80 mg and 160 mg)</u> Treatment of clinically stable adult patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours-10 days) myocardial infarction (see sections 4.4 and 5.1). <u>Heart failure (only 40 mg, 80 mg and 160 mg)</u> Treatment of adult patients with symptomatic heart failure when Angiotensin Converting Enzyme (ACE) inhibitors are not tolerated or in beta-blocker intolerant patients as add-on therapy to ACE inhibitors when mineralocorticoid receptor antagonists cannot be used (see sections 4.2, 4.4, 4.5 and 5.1). <u>Oral solution 3 mg/ml</u> Treatment of hypertension in children and adolescents 6 to 18 years of age.
Pharmaco-therapeutic group (ATC Code):	C09CA03
Pharmaceutical form(s) and strength(s):	40 mg film-coated tablets 80 mg film-coated tablets 160 mg film-coated tablets 320 mg film-coated tablets 3 mg/ml oral solution

I. EXECUTIVE SUMMARY

SmPC changes are proposed in sections 4.8 and 5.1 with focus on the additional long-term clinical experience gained in paediatric patients with CKD.

No PL changes are proposed.

II. RECOMMENDATION

The following revisions of the SmPC are recommended:

Section 4.8, addition of text under header Hypertension (with bolded/italics and deletions with strike through)

The antihypertensive effect of valsartan has been evaluated in two randomised, double-blind clinical studies (each followed by an extension period or study) and one open-label study. These studies included 711 ~~561~~ paediatric patients from 6 to ***less than*** 18 years of age ***with and without chronic kidney disease (CKD), of which 560 patients received valsartan***. With the exception of isolated gastrointestinal disorders (***such as*** ~~like~~ abdominal pain, nausea, vomiting) and dizziness, no relevant differences in terms of type, frequency and severity of adverse reactions were identified between the safety profile for paediatric patients aged 6 to ***less than*** 18 years and that previously reported for adult patients.

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A pooled analysis of 560 paediatric hypertensive patients (aged 6-17 years) receiving either valsartan monotherapy [n=483] or combination antihypertensive therapy including valsartan [n=77] was conducted. Of the 560 patients, 85 (15.2%) had CKD (baseline GFR <90 mL/min/1.73m^2). Overall, 45 (8.0%) patients discontinued a study due to adverse events. Overall 111 (19.8%) patients experienced an adverse drug reaction (ADR), with headache (5.4%), dizziness (2.3%), and hyperkalemia (2.3%) being the most frequent. In patients with CKD, the most frequent ADRs were hyperkalaemia (12.9%), headache (7.1%), blood creatinine increased (5.9%), and hypotension (4.7%). In patients without CKD, the most frequent ADRs were headache (5.1%) and dizziness (2.7%). ADRs were observed more frequently in patients receiving valsartan in combination with other antihypertensive medications than valsartan alone.

Section 5.1, addition of the following text:

In a third, open label clinical study, involving 150 paediatric hypertensive patients 6 to 17 years of age, eligible patients (systolic BP ≥95th percentile for age, gender and height) received valsartan for 18 months to evaluate safety and tolerability. Out of the 150 patients participating in this study, 41 patients also received concomitant antihypertensive medication. Patients were dosed based on their weight categories for starting and maintenance doses. Patients weighing ≥18 to < 35 kg, ≥35 to < 80 kg and ≥ 80 to < 160 kg received 40 mg, 80 mg and 160 mg and the doses were titrated to 80 mg, 160 mg and 320 mg respectively after one week. One half of the patients enrolled (50.0%, n=75) had CKD with 29.3% (44) of patients having CKD Stage 2 (GFR 60 – 89 mL/min/1.73m2) or Stage 3 (GFR 30-59 mL/min/1.73m2). Mean reductions in systolic blood pressure were 14.9 mmHg in all patients (baseline 133.5 mmHg), 18.4 mmHg in patients with CKD (baseline 131.9 mmHg) and 11.5 mmHg in patients without CKD (baseline 135.1 mmHg). The percentage of patients who achieved overall BP control (both systolic and diastolic BP <95th percentile) was slightly higher in the CKD group (79.5%) compared to the non-CKD group (72.2%).

III. INTRODUCTION

On June 21, 2016, the MAH submitted information about paediatric studies completed after 26 January 2007 for Diovan, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

In addition to the clinical study report (CSR) for study CVAL489K2305, the MAH submitted the Critical Expert Overview and the Summary of Clinical Safety where pooling data from previous studies (i.e. with Studies A2302 , K2302 and K2302E1) is also presented in order to include data from additional chronic kidney disease (CKD) stage 2-3 patients as discussed with the CHMP during the Scientific Advice dated October 2013. The inclusion of those documents was agreed with the Medical Products Agency (MPA) on 24 July 2015 in order to allow the assessment of the Article 46 procedure and the fulfilment of the post-authorization measure.

The MAH stated that the submitted paediatric study data does not influence the benefit risk balance for Diovan and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study(ies)

Novartis supplied valsartan tablets of 40 mg, 80 mg, 160 mg and 320 mg for the study.

IV.2 Clinical aspects

1. Introduction

Novartis has conducted a pediatric program with valsartan which included clinical trials in children with hypertension. The program outlined in the Paediatric Investigation Plan (PIP) was agreed upon with the EMA in October 2008 and was subsequently revised in June 2009 (EMEA-000005-PIP01-07-M01). In 2009, the Paediatric Committee (PDCO) adopted a positive opinion that the studies conducted by Novartis were in compliance with the agreed PIP and that the PIP was fully completed. Following the PIP compliance verification, Novartis submitted two parallel applications, via the Article 29 procedure of Regulation 1901/2006. One application was a variation for a new pediatric indication of the Diovan® (valsartan) film-coated tablets (40, 80, 160 and 320 mg) and the other was a new line extension Marketing Authorization Application (MAA) for the newly developed liquid formulation of Diovan® (3mg/ml oral solution). Positive Opinions were granted by the Committee for Medicinal Products for Human Use (CHMP) on 15-Dec-2009 and the Commission Decisions were issued 19-Apr-2010.

During the above Article 29 procedure, a lack of long term safety data in the pediatric population both in children with or without chronic kidney disease (CKD) was noted by the CHMP. Novartis committed to perform the long-term safety study (CVAL489K2305, hereafter referred to as Study K2305) following the approval of the pediatric indication of the Diovan® (valsartan) film-coated tablets (40, 80, 160 and 320 mg). This commitment was initially proposed as a follow-up measure and is now a post-authorization measure following the implementation of the new pharmacovigilance legislation in 2012. On 26-Aug-2013, the Medical Products Agency classified Study K2305 as a Risk Management Plan (RMP) commitment Category 3 study according to the GVP Module V guideline (Annex 3 and 4).

At the EMA Scientific Advice Meeting in October 2013, EMA expressed concern about the relatively low number of CKD Stage 2 and 3 patients in Study K2305. In response, Novartis proposed to pool additional data from Studies VAL489A2302 (hereafter referred to as Study A2302) and CVAL489K2302 and its extension CVAL489K2302E1 (hereafter referred to as Study K2302 and Study K2302E1, respectively) to obtain data from at least 90 pediatric patients with baseline estimated glomerular filtration rate (eGFR) <90 mL/min/1.73m^2. This proposal was agreed by the Scientific Advice Working Party (SAWP) during its meeting from 30 Sep- 03 Oct 2013 and adopted by the CHMP during its session in October 2013 (EMA/CHMP/SAWP/607747/2013).

The [Study CVAL489K2305] met the last patient/last visit on 10-Sep-2015 and the results are being submitted to the European Competent Authorities according to Article 46 of Regulation (EC) No 1901/2006 within 6 months of study completion.

In addition to this Critical Expert Overview, Novartis issued a Summary of Clinical Safety to be submitted together with the results of Study K2305 in order to fulfill the agreement with the CHMP in the Scientific Advice held in October 2013 to pool data from previous studies (i.e. with A2302 and K2302/K2302E1) with the purpose of evaluating data from CKD patients aged 6-17 years with eGFR <90 mL/min/1.73m^2.

The objectives of this Critical Expert Overview are to provide a summary of the information on the long term safety study K2305 in accordance with Article 46 of the Regulation No 1901/2006 and to address the Post Authorisation Measure agreed by Novartis in the Letter of Undertaking dated 15-Dec-2009, following the CHMP request to the Marketing Authorisation Holder (MAH) to address the lack of long term safety data in children with or without CKD. Therefore, this report includes an overall evaluation of the long term safety and tolerability of valsartan in pediatric hypertension patients aged 6-17 years, especially with CKD.

The MAH submitted the final study report for study CVAL 489K2305 (title: Long-term safety and tolerability in pediatric hypertensive patients)

Assessor's comment:
As noted above, a lack of long term safety data in the pediatric population with or without chronic kidney disease (CKD) was noted by the CHMP when the pediatric indication was approved. Also, the MAH was expected to obtain data from at least 90 pediatric patients with baseline estimated glomerular filtration rate (eGFR) <90 mL/min/1.73m^2. In order to meet this requirement, the MAH has submitted the final study report from the long-term safety study CVAL 489K2305 as well as a pooled safety analysis from four studies into which pediatric patients with and without CKD were recruited. Data from 85 CKD patients is included. The data submitted in this package is acceptable.

2. Clinical study(ies)

Clinical study CVAL 489K2305

- **Description**

A multicenter, open-label, 18 month study to evaluate the long-term safety and tolerability of valsartan in children 6 to 17 years of age with hypertension and with or without chronic kidney disease

- **Methods**

Objective(s)

Primary objective

- To assess the long-term safety and tolerability profile of valsartan and valsartan-based treatments in children with hypertension, with or without chronic kidney disease (CKD).

Secondary objectives

- To assess the long-term efficacy of valsartan and valsartan-based treatments in reducing the mean sitting systolic blood pressure (MSSBP) and mean sitting diastolic blood pressure (MSDBP) in children with hypertension.
- To assess the long-term efficacy of valsartan and valsartan-based treatments in controlling the mean sitting systolic and diastolic blood pressure (BP) in children with hypertension. The target mean BP was <95th percentile for age, gender and height.
- To assess the effect of valsartan and valsartan-based treatments on proteinuria and estimated glomerular filtration rate (eGFR) in a subset of children with hypertension and CKD.

Study design

Open label study with 1 treatment arm and treatment duration of 18 months. The study consisted of a screening, washout and treatment phase.

Study population /Sample size

The study population consisted of male and female children aged 6 to 17 (inclusive) years with hypertension with the mean sitting systolic blood pressure (MSSBP) (mean of 3 measurements) ≥95th percentile, and ≤25% above the 95th percentile, for age, gender and height, at baseline (Visit 2), by office blood pressure measurement.

CKD patients were defined as any of the following criteria:

1. Kidney damage for ≥3 months, as defined by one or more of the criteria below, consistent with a CKD diagnosis:
    - Abnormalities in the composition of urine
    - Abnormalities in imaging tests
    - Abnormalities on kidney biopsy
2. Estimated eGFR <60 mL/min/1.73m2 (calculated by Modified Schwartz Formula) for 3 months, with or without the other signs of kidney damage described above.

Treatments

Open-label treatment: The treatment period started with a starting dose of valsartan 40, 80 or 160 mg depending on body weight at Visit 2. After one week, the dose was titrated to 80, 160 or 320 mg respectively. The study drug maintenance doses were maximum doses, and they could have been down titrated to the respective starting dose at the investigator's discretion. After down titration the investigator could have up titrated again to the maximum dose, as necessary. The start and maintenance doses of valsartan were assigned according to the 3 weight categories as follows:

Patient's weight	Starting dose	Valsartan maintenance dose
≥18 kg to <35 kg	40 mg	80 mg
≥35 kg to <80 kg	80 mg	160 mg
≥80 kg to ≤160 kg	160 mg	320 mg

Background therapy of antihypertensive medication other than RAAS blockers (e.g. calcium channel blockers, diuretics, beta blockers) were allowed from screening through the end of study. If at Week 8 or later the MSSBP and/or MSDBP was higher than 95th percentile for age, gender and height under the maximum valsartan dose according to the table above, then

amlodipine and/or hydrochlorothiazide could have been added or doses of background antihypertensive medication could have been adjusted at the discretion of the investigator.

Criteria for evaluation
Efficacy:

- Mean sitting office blood pressure (mean of 3 measurements);
  Mean sitting systolic blood pressure (MSSBP) and mean sitting diastolic blood pressure (MSDBP)
- Urine Albumin Creatinine Ratio (UACR) (in CKD patients only)

Patients classified as Stage 1 CKD who had been undergoing UACR collections continued to do so for the duration of the trial. Patients newly classified as having Stage 1 CKD after Amendment 2 were not required to begin UACR collections unless they had collections done since study entry.

Safety:

- Adverse event assessment
- Complete laboratory including cystatin C (CKD subgroup only). Patients classified as Stage 1 CKD who had cystatin C analyzed since study entry continued to have these lab results reported. Patients newly classified as having Stage 1 CKD after Amendment 2, who had not had cystatin C levels analyzed previously in the study were not required to do so.
- eGFR (For all patients eGFR was calculated using the Modified Schwartz formula; for CKD patients the eGFR was also calculated using the cystatin C value).
- Urinalysis done locally by dipstick: glucose, protein, bilirubin, ketones, leukocytes, blood
- Electrocardiogram (ECG)

Statistical Methods
Summaries and analyses were presented by patient groups per concomitant antihypertensive medication usage (with/without) and overall. The patient groups were determined by concomitant antihypertensive medication usage at any time during the treatment period. Additional analyses were performed for the subgroups of CKD, non-CKD, and non-CKD + CKD Stage 1 patients as appropriate, where CKD/non-CKD/CKD Stage 1 was the CKD status at baseline.

Safety: The primary objective of this study was to assess the safety and tolerability profile of valsartan. The assessment of safety was based mainly on the frequency of AEs and on the summary of laboratory values. Other safety data (e.g., pulse, standing blood pressures, body weight, ECG) were summarized as appropriate.

- **Results**

Number of patients (planned and analyzed): Approximately 150 patients were to be enrolled. Overall, 203 patients were screened in this study, of which 150 patients were enrolled. All patients were included in the full analysis set (FAS) and safety set (SAF). There were 41 patients who received concomitant anti-hypertensive medication at any time during the study.

Table 1 - Analysis sets, Overall population

Population	VAL + antihyp. N= 41 n (%)	VAL N=109 n (%)	Total N=150 n (%)
Full analysis set (FAS)	41 (100)	109 (100)	150 (100)
Safety set (SAF)	41 (100)	109 (100)	150 (100)

- The Full Analysis set (FAS) included all patients who entered the treatment period.
- The Safety set included all patients who received at least one dose of study medication.

Table 2 - Analysis sets, CKD patients and non-CKD patients

	CKD patients			Non-CKD patients		
Population	VAL + antihyp. N= 23 n (%)	VAL N= 52 n (%)	Total N= 75 n (%)	VAL + antihyp. N= 18 n (%)	VAL N= 57 n (%)	Total N= 75 n (%)
Full analysis set (FAS)	23 (100)	52 (100)	75 (100)	18 (100)	57 (100)	75 (100)
Safety set (SAF)	23 (100)	52 (100)	75 (100)	18 (100)	57 (100)	75 (100)

Demographic and background characteristics:
The mean age of the overall patient population was 13.36 years with the majority of patients between 12-17 years of age (70.0%). Approximately two-thirds of patients were male (66.0%) and the majority of patients were from non-European countries (80.7%).

One half of the patients enrolled (50.0%) had CKD and 29.3% of patients had CKD Stage 2 or 3. A total of 56.1% of the valsartan + antihypertensive group were CKD patients.

The mean weight was 54.4 kg and the mean BMI was 22.3 kg/m2. The MSSBP at baseline was 133.5 mmHg and the MSDBP was 80.8 mmHg. The mean Schwartz eGFR was 128.3 mL/min/1.73m2 and the majority of patients (76.0%) had eGFR ≥90 mL/min/1.73m2.

The mean age in CKD patients was slightly lower than the non-CKD patients (12.49 years vs. 14.23 years, respectively). Approximately half of CKD patients (49.3%) were Asians compared to 14.7% in non-CKD patients.

The mean weight in CKD patients was lower than non-CKD patients (43.2 kg vs. 65.6 kg, respectively). The mean BMI was also lower (20.3 kg/m2) in CKD patients compared to non-CKD patients (24.3 kg/m2). The MSSBP at baseline was slightly lower in CKD patients (131.9 mmHg) compared to non-CKD patients (135.1 mmHg). The MSDBP in CKD patients (84.9 mmHg) was higher than non- CKD patients (76.8 mmHg). As expected, the mean Schwartz eGFR was lower in CKD patients (99.7 mL/min/1.73m2) as compared to non-CKD patients (157.0 mL/min/1.73m2). Approximately half of the CKD patients (46.7%) and 1 non-CKD patient had eGFR <90 mL/min/1.73m2.

Efficacy results
All analyses were presented by patient groups per other antihypertensive medication usage (with/without) and overall. The patient groups were determined by other antihypertensive medication usage at any time during the treatment period. These 2 groups ("valsartan alone" and "valsartan + antihypertensive") were not randomized and considered to be 2 different populations since the patients in the valsartan + antihypertensive group had other antihypertensive medication usage per individual patients' conditions (e.g. further BP control) at any time during the treatment period.

Blood pressure reduction

Valsartan produced clinically significant reductions in MSSBP and MSDBP from baseline to endpoint and at each time point during the treatment period in both CKD and non-CKD patients. The mean reductions in MSSBP and MSDBP in CKD patients were greater than in non-CKD patients at all time points. At endpoint, the mean reductions from baseline in MSSBP were 14.9 mmHg in all patients, 18.4 mmHg in CKD patients and 11.5 mmHg in non-CKD patients, respectively. The baseline MSSBP was 133.5 mmHg in the overall population, 135.1 mmHg in non-CKD patients and 131.9 mmHg in CKD patients.

At endpoint, the mean reductions from baseline in MSDBP were 10.6 mmHg in all patients, 14.2 mmHg in CKD patients and 7.1 mmHg in non-CKD patients, respectively. The mean baseline MSDBP was 80.8 mmHg in the overall population, 76.8 mmHg in non-CKD patients and 84.9 mmHg in CKD patients.

Table 3 - Summary of mean change from baseline in mean sitting systolic and mean sitting diastolic blood pressure at endpoint (Full analysis set). Study K2305

VAL only N = 109		VAL + Antihyp N = 41		Total N = 150	
N	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Mean change from baseline in sitting systolic blood pressure (mmHg)					
108	-15.5 (13.35)	41	-13.3 (13.69)	149	-14.9 (13.44)
Mean change from baseline in sitting diastolic blood pressure (mmHg)					
108	-10.8 (11.45)	41	-10.3 (11.94)	149	-10.6 (11.55)

Endpoint is the Week 78 or the last post-baseline observation carried forward (LOCF) value.

Source: [Study CVAL489K2305-Table 11-7 and Table 11-9]

Blood pressure control

Valsartan was effective in achieving overall MSSBP and MSDBP control (i.e. MSSBP and MSDBP < 95th percentile for age, gender, and height with baseline MSSBP or MSDBP ≥ 95th percentile). The percentage of patients who achieved MSSBP and MSDBP control was 75.9% in the overall patient population. The percentage of patients who achieved overall MSSBP and MSDBP control was slightly higher in the CKD group (79.5%) compared to the non-CKD group (72.2%).

Proteinuria – (as assessed by Urine albumin/creatinine ratio [UACR])

Within the first 3 months, mean UACR decreased in the overall CKD population and the reduction was sustained for the duration of the study. In the majority of patients, UACR either decreased or remained the same at endpoint compared to baseline. In 43.9% of patients, UACR was reduced ≥50% from baseline and in 41.5% of patients UACR remained the same (i.e. increase or reduction of less than 50% from baseline).

Assessor's comment:

Efficacy was a secondary endpoint in the study. Clinically significant reductions in blood pressure were seen at each timepoint during the treatment period. The percentage of patients who achieved overall blood pressure control was slightly higher in the CKD population compared to the non-CKD population. Reductions in blood pressure were demonstrated in both the valsartan alone and the valsartan + antihypertensive groups. Some differences in response were observed in the valsartan monotherapy and in the patients on combined treatment but no direct comparison between the groups should be made as the groups were not randomized.
In the majority of patients, UACR either decreased or remained the same at study end compared to baseline. Within the first 3 months, mean UACR decreased in the overall CKD population and the reduction was sustained for the duration of the study.

Safety results
Valsartan was generally well tolerated in this long-term study in children 6 to 17 years of age with hypertension. The majority of events that occurred were not unexpected in the study population and/or are known to be associated with angiotensin receptor blockers. There were no reported deaths in this study.

Overall, 79.3% of patients reported an AE with a higher incidence in the valsartan + antihypertensive group (90.2%) than the valsartan alone group (75.2%). A higher percentage of CKD patients had at least 1 AE compared to non-CKD patients (85.3% vs. 73.3%, respectively). Cough, headache, pyrexia and nasopharyngitis were the most common AEs reported in the overall and CKD populations with the incidence being slightly higher in CKD patients compared to non-CKD population. The most common AEs in non-CKD patients were headache, dizziness, cough and nasopharyngitis of which dizziness was reported with a higher frequency in non-CKD patients than CKD patients. Overall, with the exception of dizziness, AEs potentially related to low blood pressure occurred infrequently. The incidence of study drug related AEs was lower in CKD patients compared to non-CKD patients (13.3% vs. 20.0%).

The incidence of SAEs and discontinuations due to AEs was higher in patients with CKD compared to the overall population. Fifteen patients (10.0%) overall experienced a non-fatal SAE of which 11 were patients with CKD. The majority of the reported SAEs in CKD patients were related to the underlying renal disease in these patients. Seventeen patients discontinued from the study due to AEs. Most of the discontinued patients had CKD (15 CKD patients). Three CKD patients each discontinued the study due to AEs of decreased glomerular filtration rate and CKD. Two CKD patients discontinued the study due to hyperkalemia. Only 2 non-CKD patients discontinued the study due to AEs.

There were few patients who had notable hematology abnormalities. As expected, in patients with underlying CKD, increases in serum potassium, creatinine, and BUN and decreases in eGFR were more commonly reported than in non-CKD patients. Overall a higher percentage of patients had a notable decrease (>25%) in eGFR in the CKD population than the non-CKD population. Overall, a slightly higher percentage of CKD patients had changes in orthostatic blood pressure compared to non-CKD patients at any post-baseline visit. There were no clinically meaningful differences between CKD and non CKD patients in vital signs or electrocardiogram (ECG) findings.

Clinical safety studies conducted in paediatric population

There are 4 studies that provide safety data for pediatric hypertensive patients aged 6-17 years with or without CKD: Study K2305, Study K2302 and the extension to the study (Study K2302E1), and Study A2302 including its long-term open-label period. An overview of the 4 studies is provided in the table below. In addition, SAE data from the ongoing study CVAL489K2306 in pediatric hypertensive patients aged 1-5 years with or without CKD are referenced in the submitted package.

Safety data from the 4 studies were pooled to obtain data for at least 90 patients with CKD, but after a common definition for CKD was applied across studies for the pooling analysis, there were 85 patients with CKD.

Table 4 – Clinical studies with valsartan that contributed with safety data

Study	Objective, population	Number of patients randomized	Treatment duration	Valsartan therapy (od)
Open-label study, not previously submitted				
K2305	Long-term safety and tolerability in pediatric hypertensive patients	150	78 weeks	Monotherapy
Active-controlled studies, previously submitted in original dossier				
K2302	Short-term safety, tolerability and efficacy in pediatric hypertensive patients	300	12 weeks	Monotherapy
K2302E1	Long-term safety, tolerability and efficacy in pediatric hypertensive patients	250 patients from K2302 continued into K2302E1	Non-CKD patients: 14 weeks CKD patients: 66 weeks[1]	Non-CKD patients: Monotherapy CKD patients: valsartan + enalapril
Placebo-controlled study, previously submitted				
A2302	Dose-response and safety in pediatric hypertensive patients	261	4 weeks double-blind, 52 weeks open-label	Monotherapy

1 Treatment duration for CKD patients was originally 66 weeks (14 weeks + 52 weeks extension); however, since there were only 3 patients enrolled in the extension phase, the study was terminated early
CKD = chronic kidney disease, od = once daily
Source: [Study CVAL489K2305], Study CVAL489K2302, Study CVAL489K2302E1, Study VAL489A2302

Assessor's comment:
Because the requirement was to include safety data from 90 paediatric CKD patients (eGFR <90 mL/min/1.73m^2) the company has submitted data from study K2305 together with pooled paediatric safety data from four studies in children. Taken together, this data base includes 85 CKD patients which is considered acceptable.

Consideration of study design, guidelines and regulatory input
The content of this section is primarily focused on Study K2305 because the study was not previously submitted; however, relevant information about previously submitted Studies A2302, K2302 and K2302E1 has been included to facilitate understanding of all studies that provided safety data for pediatric hypertensive patients (aged 6-17 years) with or without CKD.

In Study K2305, 150 pediatric patients with hypertension, with or without CKD, were evaluated over an 18-month period. A sub-analysis was performed to study the safety and tolerability of valsartan in children with CKD.

In a teleconference with CHMP in September 2010, it was agreed that the duration of exposure in the study would be 18 months and at least 40% of the population would be patients with CKD. Novartis requested follow-up Scientific Advice on 21-May-2013 to address the low rate of enrollment of CKD patients into the study and to discuss amending the protocol to revise the protocol definition of CKD to include Stage 1 patients (i.e. patients with evidence of renal disease but eGFR ≥90 mL/min/1.73m^2). In October 2013, CHMP accepted the amendment of the K2305 study protocol with regards to the CKD definition (EMA/CHMP/SAWP/607747/2013) aligning it with the latest National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines (Hogg et al 2003) while facilitating the recruitment of CKD patients.

The study design for Studies A2302, K2302 and K2302E1 including the CKD criteria in these studies is provided in the table below. The protocol for Study A2302 did not include a pre-specified definition for CKD.

The protocol for Study K2302 pre-defined patients as having CKD if they had an eGFR <90 mL/min/1.73m^2 for at least 3 months prior to study entry. Study K2302 enrolled 300 patients, 52 (17.3%) of whom were classified as having CKD based on the protocol definition provided above. Study K2302 was followed with a 14-week extension for non-CKD patients, and a 66-week extension for CKD patients (Study K2302E1). However, only 3 CKD patients continued in the 66-week extension, and this trial was terminated early.

Table 5 Overview of investigational plan and population for the included studies

Study	Age (years)	Weight (kg)	Dosing (mg) of valsartan	Definition of CKD	Other antihypertension medications used
K2305	6-17	≥18 to ≤160	**≥18kg to <35kg** 1 week : 40mg (starting dose) 77 weeks: 80mg (maintenance dose) **≥35kg to <80kg:** 1 week: 80mg (starting dose) 77 weeks: 160mg (maintenance dose) **≥80kg to ≤160kg:** 1 week :160mg (starting dose) 77 weeks: 320mg (maintenance dose)	**CKD patients were defined in protocol** as any of the following criteria: 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/1.73m^2 (calculated by Modified Schwartz Formula) for ≥3 months, with or without the other signs of kidney damage described above. **CKD is defined for the pooling analysis** as eGFR <90 mL/min/1.73m^2 at baseline. There are 36 patients with CKD based on this definition.	Washout of RAAS blockers was required prior to entering treatment period. Patients receiving antihypertensive medications other than RAAS blockers could be tapered off if MSSBP was <95th percentile for age/gender/height at screening or could continue taking medication(s) during the study if MSSBP was ≥ 95th percentile at screening. If at Week 8 or later, the MSSBP and/or MSDBP was ≥ 95th percentile for age/gender/height under the valsartan maintenance dose, then amlodipine and/or HCTZ could be added.
K2302	6-17	≥18 to ≤160	**≥18kg to <35kg:** 1 week: 40mg (starting dose) 11 weeks: 80mg (maintenance dose). **≥35kg to <80kg:** 1 week: 80mg (starting dose) 11 weeks: 160mg (maintenance dose). **≥80kg to ≤160kg:** 1 week: 160mg (starting dose) 11 weeks: 320mg (maintenance dose).	**CKD patients in protocol** were defined as the eGFR <90 mL/min/1.73m^2 for 3 months. **CKD is defined for the pooling analysis** as eGFR <90 mL/min/1.73m^2 at baseline There are 16 patients in the valsartan group with CKD based on this definition	Patients were required to discontinue/washout any prior antihypertensive medications during the screening period. No antihypertensive medications other than study drug were permitted during the study.
K2302E1	6-17	≥18 to ≤160	**≥18kg to <35kg:** 80mg **≥35kg to <80kg:**160mg **≥80kg to ≤160kg:** 320mg	**CKD was defined in the protocol** as eGFR <90 mL/min/1.73m^2 for 3 months prior to entry into Study K2302. **CKD is defined for the pooling analysis** as eGFR <90 mL/min/1.73m^2 at Study K2302 baseline. Of the patients from the K2302 valsartan group with CKD based on this definition, 12 continued into K2302E1.	Patients without CKD could receive additional antihypertensive medications with the exception of ACEi or ARBs at any time during the 14 week extension if MSSBP was ≥ 95th percentile. Patients with CKD received valsartan plus enalapril for the first 14 weeks of the extension and could then receive additional antihypertensive medications, with the exception of ACEi or ARBs, if MSSBP was ≥ 90th percentile at visit 8 (week 14).
A2302	6-16	≥20	**<35kg**: 10mg (low) 40mg (medium) 80mg (high), **≥35kg:** 20mg (low) 80mg (medium) 160mg (high)	**CKD was not pre-defined in the protocol.** **CKD is defined for the pooling analysis** as eGFR <90 mL/min/1.73m^2 at baseline. There are 33 patients in the valsartan group with CKD based on this definition.	Patients were required to discontinue/washout any prior antihypertensive medications during the screening period. No antihypertensive medications other than study drug were permitted in double-blinded period. HCTZ could be added during open-label period.

RAAS = Renin-angiotensin-aldosterone system, MSSBP = mean sitting systolic blood pressure, MSDBP = mean sitting diastolic blood pressure, ACEi = Angiotensin converting enzyme inhibitor, ARB = Angiotensin receptor blocker, HCTZ = Hydrochlorothiazide.
Source: Study VAL489A2302, Study CVAL489K2302, Study CVAL489K2302E1, [Study CVAL489K2305] and [SCS-Appendix 1-Table 1.1a]

Assessor's comment:
The company has described the definition of CKD patients across the four studies contributing with safety data for valsartan in paediatric patients aged 12-17 years.

Paediatric safety cumulative data reviews

Pooling the data from the 4 studies provides an understanding of the safety profile in CKD patients treated with valsartan as a whole. The proposal for pooling data from Study K2305 with data from Studies A2302 and K2302/K2302E1 was agreed upon by the SAWP. CKD is defined for the pooled analysis as eGFR <90 mL/min/1.73m2 at baseline.

The pooled treatment groups include valsartan monotherapy alone, valsartan plus other antihypertensive medications and all valsartan. The pooled treatment groups are listed in table below.

Summaries and analyses were presented by patient groups per other antihypertensive medication usage (with/without) and overall. The patient groups were determined by other antihypertensive medication usage at any time during the treatment period. These 2 groups ("valsartan monotherapy" and "valsartan plus other antihypertensive medications") were not randomized and considered to be 2 different populations since the patients in the valsartan plus other antihypertensive medications group had additional antihypertensive medication usage per individual patients' conditions (e.g. further BP control) at any time during the treatment period. Thus, no conclusive treatment comparisons (valsartan vs. valsartan plus other antihypertensive medication) can be made and any interpretation for the differences observed between these two groups should be made with caution.

For the production of the pooled analyses, LLT (low level term) codes were mapped to MedDRA Version 18.1, the latest version available at the time of reporting.

AE data from individual studies were pooled and are summarized. Only AEs which occurred on or after the first dose of study drug were summarized. Adverse events occurring in the randomized withdrawal phase of Study A2302, whether occurring in patients on valsartan treatment or placebo treatment, were included in the valsartan groups in the summaries as a conservative approach.

Table 6 – Pooled treatment groups, Diovan paediatric safety studies

Pooled treatment group	Comments
Valsartan monotherapy (Val mono)	No antihypertensive medications other than study drug were used during the entire study.
Valsartan plus other antihypertensive medications (Val AHY)	In Study K2305, patients receiving antihypertensive medications other than RAAS blockers could continue taking medication(s) during the study if MSSBP was ≥ 95th percentile at screening. If at Week 8 or later, the MSSBP and/or MSDBP was ≥ 95th percentile for age/gender/height under the valsartan maintenance dose, then amlodipine and/or HCTZ could be added.
	In Study K2302E1, patients without CKD could receive additional antihypertensive medications with the exception of ACEi or ARBs at any time during the 14 week extension if MSSBP was ≥ 95th percentile. Patients with CKD received valsartan plus enalapril for the first 14 weeks of the extension and could then receive additional antihypertensive medication(s), with the exception of ACEi or ARBs, if MSSBP was ≥ 90th percentile at visit 8 (Week 14).
	In Study A2302, HCTZ could be added during the open-label period.
All valsartan (All Val)	Val Mono group plus Val AHY group

RAAS = Renin-angiotensin-aldosterone system, MSSBP/MSDBP = mean sitting systolic/diastolic blood pressure, ACEi = Angiotensin converting enzyme inhibitor, ARB = Angiotensin receptor blocker, HCTZ = Hydrochlorothiazide.

Source: [SCS-Table 1-3]

Assessor's comment:
The company has presented how the pooled treatment groups have been defined. Because of this pooling, valsartan monotherapy and those on combined treatment (Valsartan plus other antihypertensive medications) are not randomised groups. Therefore, interpretation of differences between these two groups should be made with caution.

Overview of safety in pooled populations

This Clinical Expert Overview provides a summary of:

- demography and baseline characteristics
- exposure
- adverse events (AEs) and serious AEs (SAEs)
- laboratory data
- vital signs (orthostatic blood pressure changes)

The safety data presented in each of the sections are from the overall pooled population followed by the CKD and non-CKD patient population subgroups.

Comparisons of safety data are made for CKD and non-CKD patients to provide context for interpretation of safety in the CKD subgroup.

Demographics and baseline disease characteristics

Selected demographic and baseline characteristics by baseline eGFR are provided in the table below.

Table 7 - Selected demographics by category of baseline eGFR

	Baseline eGFR < 90mL/min/1.73m^2			Baseline eGFR ≥ 90mL/min/1.73m^2		
Variable	**Val Mono N= 61**	**Val AHY N= 24**	**All Val N= 85**	**Val Mono N = 422**	**Val AHY N= 53**	**All Val N= 475**
Age (years)						
n	61	24	85	422	53	475
Mean (SD)	12.42 (2.938)	12.84 (3.491)	12.54 (3.089)	12.20 (3.089)	12.40 (2.995)	12.22 (3.076)
Min-max	6.28-17.00	6.82-17.68	6.28-17.68	6.00-17.95	6.62-17.74	6.00-17.95
Gender n (%)						
Male	31 (50.8)	12 (50.0)	43 (50.6)	261 (61.8)	38 (71.7)	299 (62.9)
Female	30 (49.2)	12 (50.0)	42 (49.4)	161 (38.2)	15 (28.3)	176 (37.1)
Race n (%)						
Caucasian	37 (60.7)	12 (50.0)	49 (57.6)	229 (54.3)	24 (45.3)	253 (53.3)
Black	4 (6.6)	0	4 (4.7)	130 (30.8)	1 (1.9)	131 (27.6)
Asian	10 (16.4)	6 (25.0)	16 (18.8)	29 (6.9)	19 (35.8)	48 (10.1)
Native American	9 (14.8)	5 (20.8)	14 (16.5)	14 (3.3)	4 (7.5)	18 (3.8)
Other	1 (1.6)	1 (4.2)	2 (2.4)	20 (4.7)	5 (9.4)	25 (5.3)
Region group n (%)						
Europe	32 (52.5)	13 (54.2)	45 (52.9)	168 (39.8)	19 (35.8)	187 (39.4)
Rest of the world	29 (47.5)	11 (45.8)	40 (47.1)	254 (60.2)	34 (64.2)	288 (60.6)

Pooled population includes studies VAL489A2302, CVAL489K2302, CVAL489K2302E1 and CVAL489K2305.
eGFR category: baseline eGFR < 90mL/min/1.73m^2, baseline eGFR ≥ 90mL/min/1.73m^2.
Source: [SCS-Appendix 1-Table 3.1a]

Table 7 - Selected demographics by category of baseline eGFR, cont.

	Baseline eGFR < 90mL/min/1.73m^2			Baseline eGFR ≥ 90mL/min/1.73m^2		
	Val Mono N=61	Val AHY N=24	All Val N=85	Val Mono N=422	Val AHY N=53	All Val N=475
Weight (kg)						
n	61	24	85	422	53	475
Mean (SD)	42.2 (17.01)	46.3 (18.21)	43.3 (17.35)	67.3 (31.21)	54.4 (20.67)	65.9 (30.48)
Min-max	18.6-91.9	21.8-74.5	18.6-91.9	18.0-196.0	20.9-101.4	18.0-196.0
Height (cm)						
n	61	24	85	422	53	475
Mean (SD)	143.4 (18.20)	145.5 (19.10)	144.0 (18.37)	155.6 (18.29)	151.1 (17.83)	155.1 (18.28)
Min-max	110.0-176.0	115.0-179.0	110.0-179.0	111.0-192.0	115.0-181.0	111.0-192.0
BMI (kg/m^2)						
n	61	24	85	422	53	475
Mean (SD)	19.8 (5.04)	21.1 (5.28)	20.2 (5.11)	26.7 (9.06)	22.9 (5.33)	26.2 (8.80)
Min-max	12.7-38.3	14.3-34.7	12.7-38.3	9.8-67.8	14.2-33.9	9.8-67.8
Mean Sitting Systolic Blood Pressure (mmHg)						
n	61	24	85	422	53	475
Mean (SD)	132.4 (11.67)	137.9 (14.65)	134.0 (12.74)	132.8 (9.92)	133.8 (11.12)	132.9 (10.05)
Min-max	110.0-160.0	115.0-185.0	110.0-185.0	107.7-162.7	109.7-160.7	107.7-162.7
Mean Sitting Diastolic Blood Pressure (mmHg)						
n	61	24	85	422	53	475
Mean (SD)	84.6 (12.03)	85.5 (16.12)	84.8 (13.22)	77.1 (9.91)	81.5 (12.11)	77.5 (10.26)
Min-max	59.7-108.7	59.7-137.0	59.7-137.0	48.3-110.7	54.3-110.0	48.3-110.7
Baseline Modified Schwartz eGFR category 1 (mL/min/1.73m^2) n (%)						
eGFR < 30	1 (1.6)	0	1 (1.2)	-	-	-
eGFR ≥30 to <60	25 (41.0)	12 (50.0)	37 (43.5)	-	-	-
eGFR ≥60 to <90	35 (57.4)	12 (50.0)	47 (55.3)	-	-	-
eGFR ≥ 90	-	-	-	422 (100.0)	53 (100.0)	475 (100.0)

Pooled population includes studies VAL489A2302, CVAL489K2302, CVAL489K2302E1 and CVAL489K2305.
eGFR category: baseline eGFR < 90mL/min/1.73m^2, baseline eGFR ≥ 90mL/min/1.73m^2.
Source: [SCS-Appendix 1-Table 3.2a]

Assessor's comment:
In addition to eGFR, differences in baseline characteristics between the CKD and non-CKD subgroups were observed for weight and BMI.

Overall extent of exposure

A total of 413 (73.8%) patients in the pooled population received valsartan for at least 182 days (26 weeks), 297 (53.0%) patients for at least 364 days (52 weeks), and 82 (14.6%) patients for

at least 546 days (78 weeks). A greater percentage of Val AHY patients (32.5%) than Val Mono patients (11.8%) received valsartan for at least 78 weeks.
The mean duration of exposure for All Val was 311.9 days. The mean duration of exposure was greater for the Val AHY group (340.1 days) than for the Val Mono group (307.4 days).

The pooled exposure data by baseline eGFR value show that patients in the included studies had long-term exposure to valsartan (Table 3-6). Mean exposure in days was similar for CKD and non-CKD patients (300.8 and 313.6 days, respectively). In non-CKD patients, exposure was longer in the Val AHY group (357.8 days) compared to the Val Mono group (308.0 days).
More than 50% of patients received valsartan for at least 52 weeks, which was similar in the CKD and non-CKD subgroups, and approximately 15% of CKD and non-CKD patients received valsartan for at least 78 weeks.

Table 8 - Duration of exposure to valsartan by category of baseline eGFR (Safety set)

	Baseline eGFR < 90mL/min/1.73m^2			Baseline eGFR ≥ 90mL/min/1.73m^2		
Duration of exposure	**Val Mono N =61**	**Val AHY N =24**	**All Val N =85**	**Val Mono N =420**	**Val AHY N =53**	**All Val N =473**
Days of Exposure n (%)						
> 0	61 (100)	24 (100)	85 (100)	420 (100)	53 (100)	473 (100)
≥ 7 (1 week)	61 (100)	23 (95.8)	84 (98.8)	414 (98.6)	52 (98.1)	466 (98.5)
≥ 14 (2 weeks)	59 (96.7)	23 (95.8)	82 (96.5)	407 (96.9)	52 (98.1)	459 (97.0)
≥ 28 (4 weeks)	53 (86.9)	23 (95.8)	76 (89.4)	397 (94.5)	51 (96.2)	448 (94.7)
≥ 42 (6 weeks)	53 (86.9)	22 (91.7)	75 (88.2)	393 (93.6)	51 (96.2)	444 (93.9)
≥ 56 (8 weeks)	52 (85.2)	22 (91.7)	74 (87.1)	391 (93.1)	51 (96.2)	442 (93.4)
≥ 84 (12 weeks)	47 (77.0)	21 (87.5)	68 (80.0)	375 (89.3)	50 (94.3)	425 (89.9)
≥ 182 (26 weeks)	42 (68.9)	14 (58.3)	56 (65.9)	317 (75.5)	38 (71.7)	355 (75.1)
≥ 266 (38 weeks)	36 (59.0)	12 (50.0)	48 (56.5)	235 (56.0)	30 (56.6)	265 (56.0)
≥ 364 (52 weeks)	32 (52.5)	11 (45.8)	43 (50.6)	224 (53.3)	28 (52.8)	252 (53.3)
≥ 392 (56 weeks)	19 (31.1)	9 (37.5)	28 (32.9)	147 (35.0)	27 (50.9)	174 (36.8)
≥ 448 (64 weeks)	14 (23.0)	8 (33.3)	22 (25.9)	76 (18.1)	25 (47.2)	101 (21.4)
≥ 462 (66 weeks)	14 (23.0)	8 (33.3)	22 (25.9)	76 (18.1)	25 (47.2)	101 (21.4)
≥ 546 (78 weeks)	8 (13.1)	5 (20.8)	13 (15.3)	49 (11.7)	20 (37.7)	69 (14.6)
Descriptive Statistics (Days)						
n	61	24	85	420	53	473
Mean (SD)	300.7 (192.33)	300.9 (206.50)	300.8 (195.19)	308.0 (166.03)	357.8 (193.74)	313.6 (169.86)
Min-Max	10-621	2-556	2-621	1-650	6-582	1-650

Pooled population includes studies VAL489A2302, CVAL489K2302, CVAL489K2302E1 and CVAL489K2305.
Source: [SCS-Appendix 1-Table 2.1a].

Adverse Events

Overall population
An overall summary of AEs, SAEs, deaths and other significant AEs is provided in table below.

Most patients (82.3%) had at least one AE. There were no patient deaths. SAEs were reported for 7.9% of patients and discontinuation of study drug due to an AE was reported for 8.0% of patients.
AEs, SAEs, AE discontinuations, and suspected related AEs were reported more frequently in patients receiving Val AHY compared to patients who received Val Mono. It should be noted that the number of patients in the Val AHY group was small. In addition, there was a greater percentage of patients with a baseline eGFR <90 mL/min/1.73m^2 in the Val AHY group (31.2%) than in the Val Mono group (12.6%).
Furthermore, 21 patients (27.3%) in the Val AHY group received dual RAAS therapy with valsartan plus the ACEi enalapril as part of the study design in Study K2302E1.

Table 9 – Overview of Adverse Events (Safety set)

Variable	Val Mono N=483 n (%)	Val AHY[1] N=77 n (%)	All Val N=560 n (%)
Patients with any AE(s)	393 (81.4)	68 (88.3)	461 (82.3)
Suspected related AEs	84 (17.4)	27 (35.1)	111 (19.8)
Serious AEs or AE discontinuations			
Death	0	0	0
Serious AE(s)	27 (5.6)	17 (22.1)	44 (7.9)
Discontinued due to AE(s)	31 (6.4)	14 (18.2)	45 (8.0)
Discontinued due to Serious AE(s)	6 (1.2)	6 (7.8)	12 (2.1)
Discontinued due to non-Serious AE(s)	25 (5.2)	9 (11.7)	34 (6.1)

Pooled population includes studies VAL489A2302, CVAL489K2302, CVAL489K2302E1 and CVAL489K2305.
[1] There were 21 CKD patients in K2302E1 who received valsartan plus enalapril as part of the study design.
Source: [SCS-Appendix 1-Table 4.1, Table 4.4, Table 4.5, Table 4.6, Table 4.7]

The most frequent AEs were headache (29.1%), cough (18.0%), nasopharyngitis (17.5%), pyrexia (16.4%), and upper respiratory tract infection (12.1%).

Some AEs were observed more frequently in patients receiving Val AHY than Val Mono including hyperkalemia, hypotension, cough, pyrexia and dizziness. In particular, hyperkalemia was reported for 15 (2.7%) patients: 7 (1.4%) Val Mono and 8 (10.4%) Val AHY. In the Val AHY group, 7 of the 8 patients with hyperkalemia were CKD patients receiving valsartan plus enalapril in Study K2302E1. Similarly, hypotension was reported for 12 (2.1%) patients: 6 (1.2%) Val Mono and 6 (7.8%) Val AHY. In the Val AHY group, 3 of the 6 patients with hypotension were CKD patients who received valsartan plus enalapril.

The most frequent suspected related AEs were headache (5.4%), dizziness (2.7%) and hyperkalemia (2.3%). These were more common in the Val AHY group, most notably for hyperkalemia (1.0% Val Mono and 10.4% Val AHY) and also for suspected related hypotension which was reported overall in 1.4% of patients (0.4% Val Mono and 7.8% Val AHY). Many of the patients in Val AHY group had underlying CKD and some also received valsartan in combination with an ACEi as noted in the previous paragraph.

Electrocardiogram QT prolonged, suspected to be related to study drug, was reported for 6 patients (1.1%). These patients were all in Study A2302 which did not have a comparator arm and was the only study that evaluated ECG by QT interval. Five of the events occurred in the open-label phase and 1 occurred in the double-blind phase. Four of the 6 cases of QT

prolongation were confirmed by the Central ECG Reader. For 2 of the 4 confirmed cases, the QT interval was prolonged at baseline, and for 3 of the 4 cases, the QT prolongation resolved at the end of the study. For the 1 remaining case, baseline values for QTcBa and QTcF were 387 msec and 395 msec and final visit values were 464 msec and 422 msec, respectively. In only 1 of these 6 patients did the QT interval exceed the notable criteria (QTcBa >480 msec) with a QTcBa value of 481 msec during the double-blind phase which decreased to 448 msec while continuing in the open-label phase. None of the events were SAEs and none resulted in study discontinuation.

Severe AEs were reported for 8.6% of patients, most often within the infections and infestations system organ class (3.4% of patients). No severe infections were reported in more than 3 patients (0.5%) overall. Severe infections reported for more than 1 patient were: gastroenteritis (3 patients), and sinusitis, tonsillitis, and pyelonephritis (2 patients each).

SAEs were reported for 7.9% of patients in completed studies. Hyperkalemia was reported as an SAE for 5 patients (0.9%), 4 of whom had CKD. Lupus nephritis was reported for 4 patients (0.7%), 1 of whom was a CKD patient. All 4 patients were in Study K2305 and had lupus nephritis at baseline. Two patients each (0.4%) had SAEs of blood creatinine increased (both CKD patients) and hypotension (1 CKD patient). Although overall incidence of SAEs was higher in the Val AHY group (22.1%) compared to the Val Mono group (5.6%), the number of patients with each reported SAE was small in each group (≤3 patients).

AEs leading to permanent discontinuation of study drug were reported for 8.0% of patients. Hyperkalemia and hypotension were the most common (10 patients (1.8%) and 5 patients (0.9%), respectively). Overall, AEs leading to discontinuation occurred more frequently in Val AHY than in Val Mono, largely due to hyperkalemia and hypotension. Information about these events in CKD and non-CKD patients is provided later in this section.

CKD and non-CKD patients

An overall summary of AEs, SAEs, deaths and other significant AEs by category of baseline eGFR is provided in the table below. Most CKD and non-CKD patients had at least one AE: 91.8% and 80.5%, respectively. SAEs were reported in more CKD than non-CKD patients (22.4% and 5.3%, respectively). Discontinuation due to an AE was also more common in CKD patients than non-CKD patients (31.8% and 3.8%, respectively). In both CKD and non-CKD patients, incidences of SAEs, discontinuations due to AEs, and suspected related AEs, were higher in the Val AHY group compared to the Val Mono group. As noted previously, comparisons between the Val AHY and Val Mono groups must be interpreted cautiously because the groups were not randomized and the number of patients receiving Val AHY is small.

Table 10 - Overview of AEs by category of baseline eGFR (Safety set)

	Baseline eGFR < 90mL/min/1.73m^2			**Baseline eGFR ≥ 90mL/min/1.73m^2**		
Variable	**Val Mono N=61 n (%)**	**Val AHY[1] N=24 n (%)**	**All Val N=85 n (%)**	**Val Mono N=420 n (%)**	**Val AHY[1] N=53 n (%)**	**All Val N=473 n (%)**
Patients with any AE(s)	57 (93.4)	21 (87.5)	78 (91.8)	334 (79.5)	47 (88.7)	381 (80.5)
Suspected related AEs	14 (23.0)	12 (50.0)	26 (30.6)	69 (16.4)	15 (28.3)	84 (17.8)
Serious AEs or AE discontinuations						
Death	0	0	0	0	0	0

Serious AE(s)	11 (18.0)	8 (33.3)	19 (22.4)	16 (3.8)	9 (17.0)	25 (5.3)
Discontinued due to AE(s)	16 (26.2)	11 (45.8)	27 (31.8)	15 (3.6)	3 (5.7)	18 (3.8)
Discontinued due to Serious AE(s)	5 (8.2)	4 (16.7)	9 (10.6)	1 (0.2)	2 (3.8)	3 (0.6)
Discontinued due to non-Serious AE(s)	11 (18.0)	8 (33.3)	19 (22.4)	14 (3.3)	1 (1.9)	15 (3.2)

Pooled population includes studies VAL489A2302, CVAL489K2302, CVAL489K2302E1 and CVAL489K2305.
[1] There were 21 CKD patients in K2302E1 who received valsartan plus enalapril as part of the study design. When the pooling analysis definition was applied, 9 of these patients were classified as CKD patients and 12 were classified as non-CKD patients.
eGFR category: baseline eGFR < 90 mL/min/1.73m^2, baseline eGFR ≥ 90 mL/min/1.73m^2.
Source: [SCS-Appendix 1-Table 4.1a, Table 4.4a, Table 4.5a, Table 4.6a, Table 4.7a]

The most common AEs for CKD and non-CKD patients, respectively, were cough (29.4% and 16.1%), headache (23.5% and 30.0%), nasopharyngitis (21.2% and 16.9%), and pyrexia (20.0% and 15.6%).

In CKD patients, hyperkalemia was reported for 12.9% of patients and was reported for more patients in the Val AHY group (8 patients, 33.3%) than in the Val Mono group (3 patients, 4.9%). Blood creatinine increased and chronic kidney disease were reported for 7.1% (n=6) and 5.9% (n=5) of CKD patients, respectively; each occurred in 3 patients in the Val AHY group (12.5%). Hypotension was reported for 4 CKD patients (4.7%), all in the Val AHY group. Dizziness occurred in 11.8% of CKD patients in similar proportions in the Val Mono and Val AHY groups.

In non-CKD patients, there were 4 (0.8%) patients with hyperkalemia, all in the Val Mono group. There were 8 (1.7%) non-CKD patients with hypotension: 6 (1.4%) in the Val Mono group and 2 (3.8%) in the Val AHY group. There were no AEs of blood creatinine increased or chronic kidney disease in non-CKD patients. Dizziness occurred in 9.9% of non-CKD patients with a greater proportion of patients in the Val AHY group than Val Mono group.

A summary of AEs suspected to be related to study treatment in 1% or more CKD or non-CKD patients in any group is provided in tables below. A greater percentage of CKD than non-CKD patients had at least one suspected related AE (30.6% and 17.8%, respectively). The most common suspected related AEs in CKD patients were hyperkalemia (12.9%), headache (7.1%), blood creatinine increased (5.9%), and hypotension (4.7%). In non-CKD patients, the most frequent suspected related AEs were headache (5.1%) and dizziness (2.7%).

In patients with CKD, AEs suspected to be related to study drug that were observed more frequently in patients receiving Val AHY than Val Mono included hyperkalemia and hypotension.

Table 11 - Number (%) of patients with adverse events suspected to be related to study drug (>= 1% for any treatment group) by preferred term by category of baseline eGFR (Safety set)

Baseline eGFR < 90 mL/min/1.73m^2

Preferred term	Val Mono N=61 n (%)	Val AHY[1] N=24 n (%)	All Val N=85 n (%)
Number (%) of patients with at least one AE	**14 (23.0)**	**12 (50.0)**	**26 (30.6)**
Hyperkalaemia	3 (4.9)	8 (33.3)	11 (12.9)
Headache	3 (4.9)	3 (12.5)	6 (7.1)
Blood creatinine increased	2 (3.3)	3 (12.5)	5 (5.9)

Hypotension	0	4 (16.7)	4 (4.7)
Chronic kidney disease	0	2 (8.3)	2 (2.4)
Dizziness	1 (1.6)	1 (4.2)	2 (2.4)
Nausea	2 (3.3)	0	2 (2.4)
Abdominal pain	0	1 (4.2)	1 (1.2)
Altered state of consciousness	1 (1.6)	0	1 (1.2)
Asthenia	0	1 (4.2)	1 (1.2)
Blood potassium increased	1 (1.6)	0	1 (1.2)
Blood urea increased	0	1 (4.2)	1 (1.2)
Cough	1 (1.6)	0	1 (1.2)
Dehydration	1 (1.6)	0	1 (1.2)
Eye swelling	1 (1.6)	0	1 (1.2)
Feeling hot	0	1 (4.2)	1 (1.2)
Malaise	0	1 (4.2)	1 (1.2)
Nephrotic syndrome	1 (1.6)	0	1 (1.2)
Orthostatic hypotension	1 (1.6)	0	1 (1.2)
Peripheral swelling	1 (1.6)	0	1 (1.2)
Proteinuria	1 (1.6)	0	1 (1.2)
Rash	1 (1.6)	0	1 (1.2)
Vertigo	0	1 (4.2)	1 (1.2)

Baseline eGFR ≥90 mL/min/1.73m^2

Preferred term	**Val Mono N=420 n (%)**	**Val AHY[1] N=53 n (%)**	**All Val N=473 n (%)**
Number (%) of patients with at least one AE	**69 (16.4)**	**15 (28.3)**	**84 (17.8)**
Headache	20 (4.8)	4 (7.5)	24 (5.1)
Dizziness	9 (2.1)	4 (7.5)	13 (2.7)
Electrocardiogram QT prolonged	6 (1.4)	0	6 (1.3)
Hypotension	2 (0.5)	2 (3.8)	4 (0.8)
Orthostatic hypotension	4 (1.0)	0	4 (0.8)
Vomiting	4 (1.0)	0	4 (0.8)
Abdominal pain	1 (0.2)	1 (1.9)	2 (0.4)
Asthenia	1 (0.2)	1 (1.9)	2 (0.4)
Micturition urgency	1 (0.2)	1 (1.9)	2 (0.4)
Nausea	1 (0.2)	1 (1.9)	2 (0.4)
Vertigo	0	2 (3.8)	2 (0.4)
Vision blurred	1 (0.2)	1 (1.9)	2 (0.4)

Arthralgia	0	1 (1.9)	1 (0.2)
Flushing	0	1 (1.9)	1 (0.2)
Gastroenteritis	0	1 (1.9)	1 (0.2)
Hypertensive crisis	0	1 (1.9)	1 (0.2)
Insomnia	0	1 (1.9)	1 (0.2)
Nasal congestion	0	1 (1.9)	1 (0.2)
Nasopharyngitis	0	1 (1.9)	1 (0.2)
Polycythaemia	0	1 (1.9)	1 (0.2)
Rhinitis allergic	0	1 (1.9)	1 (0.2)

Pooled population studies VAL489A2302, CVAL489K2302, CVAL489K2302E1 and CVAL489K2305.

[1] There were 21 CKD patients in K2302E1 who received valsartan plus enalapril as part of the study design. When the pooling analysis definition was applied, 9 of these patients were classified as CKD patients and 12 were classified as non-CKD patients.

Preferred terms are sorted in descending frequency of occurrence within the All Val group.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category.
eGFR category: baseline eGFR < 90 mL/min/1.73m^2, baseline eGFR ≥ 90 mL/min/1.73m^2.
Source: [SCS-Appendix 1-Table 4.4a]

Severe AEs were reported for 22.4% of CKD patients and 6.1% of non-CKD patients, and as for the overall population, severe events were most commonly in the infections and infestations class. For individual preferred terms under infections, incidences were low and did not show any obvious differences between CKD and non-CKD patients, or Val Mono and Val AHY patients.

Overall, SAEs were reported in more CKD than non-CKD patients in completed studies. Hyperkalemia was reported as an SAE for 5 (0.9%) patients, 4 of whom were CKD patients. Lupus nephritis was reported for 4 (0.7%) patients, including 1 CKD patient, all of whom had a history of lupus nephritis as previously described in this section for the summary of overall patients. Blood creatinine increased was reported for 2 CKD patients and hypotension was reported for 2 patients (1 CKD patient). No notable differences in SAEs by preferred terms were observed due to the small numbers of patients with SAEs and differences in sizes of the Val AHY group compared to Val Mono group.

Discontinuations due to AEs were also more common in CKD patients than non-CKD patients. Hyperkalemia, the most frequent AE leading to discontinuation in the overall population was also the most common AE leading to discontinuation in CKD patients (8 patients; 7 in the Val AHY group). Hypotension resulted in discontinuation for 4 CKD patients, all of whom were in the Val AHY group. All of the patients discontinued for blood creatinine increased, chronic kidney disease and glomerular filtration rate decreased (3 patients each) were CKD patients. The 1 patient with an AE of blood potassium increased was also a CKD patient. Differences between the Val Mono and Val AHY groups should be interpreted with caution, as noted for SAEs above.

Assessor's comment:
The observed pattern of AEs in the pooled population did not reveal any significant unexpected findings. Most of the frequently reported AEs, and related AEs, are listed in the SmPC. SAEs and discontinuations due to AEs were reported more frequently in CKD patients than in non-CKD patients.

Adverse Events associated with safety concerns included in the RMP
Analyses of the pooled population were performed for the events identified in the Diovan

pediatric RMP as important identified or potential risks that were to be closely monitored in PSURs. These searches were made for the following safety concerns:

Identified risks

- Hyperkalemia category
  Preferred terms: blood potassium abnormal, blood potassium increased, and hyperkalemia
- Hypotension category
  High level group term: Decreased and nonspecific blood pressure disorders and shock
  Preferred terms: altered state of consciousness, consciousness fluctuating, depressed level of consciousness, loss of consciousness, blood pressure abnormal, blood pressure decreased, blood pressure ambulatory abnormal, blood pressure systolic abnormal, blood pressure diastolic abnormal, blood pressure orthostatic abnormal, blood pressure fluctuation, blood pressure ambulatory decreased, blood pressure systolic decreased, blood pressure diastolic decreased, blood pressure orthostatic decreased

Potential risks

- Elevation of liver function values (SMQ broad: Drug related hepatic disorders-comprehensive search), renal impairment (SMQ broad: Acute renal failure), and hypersensitivity including angioedema and serum sickness (SMQ narrow and broad: Angioedema and Anaphylactic reaction).

Important identified and potential risks by risk category are summarized by baseline eGFR category in the table below.

Table 12 - Important identified and potential risks by risk category and by category of baseline eGFR (Safety set)

	Baseline eGFR < 90mL/min/1.73m^2			**Baseline eGFR ≥ 90mL/min/1.73m^2**		
Category	**Val Mono N=61 n (%)**	**Val AHY[1] N=24 n (%)**	**All Val N=85 n (%)**	**Val Mono N=420 n (%)**	**Val AHY[1] N=53 n (%)**	**All Val N=473 n (%)**
Patients with any important identified risk	**11 (18.0)**	**10 (41.7)**	**21 (24.7)**	**52 (12.4)**	**11 (20.8)**	**63 (13.3)**
Hypotension	8 (13.1)	5 (20.8)	13 (15.3)	47 (11.2)	11 (20.8)	58 (12.3)
Hyperkalemia	3 (4.9)	8 (33.3)	11 (12.9)	5 (1.2)	0	5 (1.1)
Patients with any important potential risk	**8 (13.1)**	**5 (20.8)**	**13 (15.3)**	**12 (2.9)**	**3 (5.7)**	**15 (3.2)**
Renal impairment	7 (11.5)	5 (20.8)	12 (14.1)	4 (1.0)	2 (3.8)	6 (1.3)
Anaphylactic reaction	2 (3.3)	1 (4.2)	3 (3.5)	7 (1.7)	1 (1.9)	8 (1.7)
Angioedema	2 (3.3)	1 (4.2)	3 (3.5)	7 (1.7)	1 (1.9)	8 (1.7)
Elevation of liver function values	0	0	0	2 (0.5)	0	2 (0.4)

In the identified risk category of hypotension, 13 CKD patients (15.3%) and 58 non-CKD patients (12.3%) had one or more preferred terms identified by the search. In the identified risk category of hyperkalemia, 11 CKD patients (12.9%) and 5 non-CKD patients (1.1%) had one or more preferred terms identified by the search.

In the potential risk category of renal impairment, 12 (14.1%) CKD patients and 6 (1.3%) non-CKD patients had one or more preferred terms identified by the search. Incidences of other potential risks were low and similar between CKD and non-CKD patients. In CKD patients, higher percentages of patients had events in these risk categories in the Val AHY group compared to the Val Mono group.

Laboratory results

Overall population
Laboratory hematology and biochemistry data were summarized for the safety population.

Clinically notable criteria for pooled hematology and biochemistry results were defined based on percent changes during the treatment period relative to baseline values. In addition, selected notable criteria were defined for pooled biochemistry summaries, as described in the interpretation of results within this section. For hematology parameters, the incidences of clinically notable percent changes from baseline at any time during the treatment period were <1% for hematocrit, hemoglobin, red blood cells (RBCs), and <2% for platelet count. Variability and shifts in white blood cell (WBC) counts that were observed were consistent with the incidence of concomitant transient infections in the studied pediatric population.

A summary of patients with clinically notable percent changes from baseline in biochemistry values at any time during the treatment period is provided in the table below. Overall, 17.2% of patients had a >50% increase in BUN, 16.3% of patients had a >20% increase in potassium, 15.3% of patients had a >25% decrease in Schwartz eGFR and 9.6% of patients had a >50% increase in creatinine. For these same parameters, clinically notable percent changes from baseline were observed more frequently in patients receiving Val AHY than Val Mono.

Table 13 - Number (%) of patients with clinically notable biochemistry values at any time during treatment period (Safety set)

Parameter Criterion	Val Mono N=483 n/m (%)	Val AHY[1] N=77 n/m (%)	All Val N=560 n/m (%)
Albumin			
>25% decrease	3/468 (0.6)	3/77 (3.9)	6/545 (1.1)
>50% increase	4/468 (0.9)	4/77 (5.2)	8/545 (1.5)
Bilirubin (total)			
>100% increase	57/465 (12.3)	12/76 (15.8)	69/541 (12.8)
Blood Urea Nitrogen (BUN)			
>50% increase	72/468 (15.4)	22/77 (28.6)	94/545 (17.2)
>100% increase	15/468 (3.2)	11/77 (14.3)	26/545 (4.8)
Calcium			
>10% decrease	21/467 (4.5)	6/77 (7.8)	27/544 (5.0)
>10% increase	40/467 (8.6)	8/77 (10.4)	48/544 (8.8)
Chloride			
>10% decrease	4/471 (0.8)	3/77 (3.9)	7/548 (1.3)
>10% increase	6/471 (1.3)	0/77	6/548 (1.1)
Creatinine			
>50% increase	39/473 (8.2)	14/77 (18.2)	53/550 (9.6)
>100% increase	6/473 (1.3)	3/77 (3.9)	9/550 (1.6)
Glucose			
>50% decrease	10/466 (2.1)	2/77 (2.6)	12/543 (2.2)
>50% increase	17/466 (3.6)	2/77 (2.6)	19/543 (3.5)

Potassium			
>20% decrease	21/471 (4.5)	6/76 (7.9)	27/547 (4.9)
>20% increase	62/471 (13.2)	27/76 (35.5)	89/547 (16.3)
SGOT (AST)			
>150% increase	4/466 (0.9)	1/77 (1.3)	5/543 (0.9)
SGPT (ALT)			
>150% increase	12/467 (2.6)	1/76 (1.3)	13/543 (2.4)
Schwartz eGFR			
>25% decrease	62/473 (13.1)	22/77 (28.6)	84/550 (15.3)
Sodium			
>5% decrease	15/472 (3.2)	5/77 (6.5)	20/549 (3.6)
Uric Acid			
>50% increase	20/467 (4.3)	6/77 (7.8)	26/544 (4.8)

For summaries of selected notable liver function test parameters (total bilirubin, SGOT/AST, and SGPT/ALT), criteria were defined relative to the upper limit of the reference range. For SGPT, 7 patients (1.3%; all in the Val Mono group) had a value >3x the upper limit of the reference range, and of these 7 cases, 1 patient (0.2%) also had an SGPT value >5x the upper limit. In 2 cases, SGPT values declined below the abnormal threshold during study treatment, in 1 case, the SGPT values returned to normal after study treatment discontinuation, and in 4 cases, repeat SGPT values were not reported. No patient had an SGOT >3x the upper limit.

For total bilirubin, 1 patient (0.2%) had a value >2x the upper limit, which was not accompanied by SGOT or SGPT increases. In addition, this patient had elevated bilirubin 6 days prior to baseline.

The categories summarized for selected notable potassium values were: >5.3, >5.5, and >6.0 mEq/L. Potassium values >5.3 mEq/L and >5.5 mEq/L occurred in 8.5% and 6.5% of patients, respectively. A total of 14 patients (2.5%) had a potassium value >6.0 mEq/L at any time during the treatment period. Incidences of each were higher in each category in the Val AHY than the Val Mono group.

CKD and non-CKD patients

As for the overall pooled safety population, hematology results in CKD and non-CKD patients were not clinically relevant.

A summary of patients with clinically notable biochemistry values (based on percent change relative to baseline) during the treatment period is shown in the table below. With respect to renal parameters, a greater percentage of CKD patients had clinically notable percent changes from baseline in albumin, BUN, creatinine, and potassium, and a notable decrease in eGFR, than non-CKD patients. A greater percentage of CKD patients also had clinically notable changes in calcium (increases or decreases) than non-CKD patients.

As in the overall population, clinically notable percent changes from baseline were observed more frequently in CKD patients receiving Val AHY than Val Mono for increases in BUN, creatinine, potassium, and decreases in Schwartz eGFR.

In non-CKD patients, clinically notable percent changes from baseline were observed more frequently in patients receiving Val AHY than Val Mono for increase in potassium and decrease in Schwartz eGFR.

Table 14 - Number (%) of patients with clinically notable biochemistry values during treatment period by category of baseline eGFR (Safety set)

	Baseline eGFR < 90mL/min/1.73m^2			Baseline eGFR ≥ 90mL/min/1.73m^2		
Parameter Criterion	**Val Mono N=61 n/m (%)**	**Val AHY[1] N=24 n/m (%)**	**All Val N=85 n/m (%)**	**Val Mono N=420 n/m (%)**	**Val AHY[1] N=53 n/m (%)**	**All Val N=473 n/m (%)**
Albumin						
>25% decrease	0/60	1/24 (4.2)	1/84(1.2)	3/408 (0.7)	2/53 (3.8)	5/461 (1.1)
>50% increase	1/60 (1.7)	2/24 (8.3)	3/84(3.6)	3/408 (0.7)	2/53 (3.8)	5/461 (1.1)
Bilirubin (total)						
>100% increase	5/58 (8.6)	2/24 (8.3)	7/82 (8.5)	52/407 (12.8)	10/52 (19.2)	62/459 (13.5)
Blood Urea Nitrogen (BUN)						
>50% increase	11/61 (18.0)	11/24 (45.8)	22/85 (25.9)	61/407 (15.0)	11/53 (20.8)	72/460 (15.7)
>100% increase	4/61 (6.6)	6/24 (25.0)	10/85 (11.8)	11/407 (2.7)	5/53 (9.4)	16/460 (3.5)
Calcium						
>10% decrease	5/60 (8.3)	2/24 (8.3)	7/84 (8.3)	16/407(3.9)	4/53 (7.5)	20/460 (4.3)
>10% increase	8/60 (13.3)	4/24 (16.7)	12/84 (14.3)	32/407 (7.9)	4/53 (7.5)	36/460 (7.8)
Chloride						
>10% decrease	1/60 (1.7)	1/24 (4.2)	2/84 (2.4)	3/411 (0.7)	2/53 (3.8)	5/464 (1.1)
>10% increase	2/60 (3.3)	0/24	2/84 (2.4)	4/411 (1.0)	0/53	4/464 (0.9)
Creatinine						
>50% increase	5/61 (8.2)	8/24 (33.3)	13/85 (15.3)	34/412 (8.3)	6/53 (11.3)	40/465 (8.6)
>100% increase	0/61	2/24 (8.3)	2/85 (2.4)	6/412 (1.5)	1/53 (1.9)	7/465 (1.5)
Glucose						
>50% decrease	1/60 (1.7)	2/24 (8.3)	3/84 (3.6)	9/406 (2.2)	0/53	9/459 (2.0)
>50% increase	3/60 (5.0)	0/24	3/84 (3.6)	14/406 (3.4)	2/53 (3.8)	16/459 (3.5)
Potassium						
>20% decrease	3/61 (4.9)	3/24 (12.5)	6/85 (7.1)	18/410 (4.4)	3/52 (5.8)	21/462 (4.5)
>20% increase	16/61 (26.2)	12/24 (50.0)	28/85 (32.9)	46/410 (11.2)	15/52 (28.8)	61/462 (13.2)
SGOT (AST)						
>150% increase	1/60 (1.7)	0/24	1/84 (1.2)	3/406 (0.7)	1/53 (1.9)	4/459 (0.9)
SGPT (ALT)						
>150% increase	3/60 (5.0)	0/23	3/83 (3.6)	9/407 (2.2)	1/53 (1.9)	10/460 (2.2)
Schwartz eGFR						
>25% decrease	10/61 (16.4)	10/24 (41.7)	20/85 (23.5)	52/412 (12.6)	12/53 (22.6)	64/465 (13.8)
Sodium						
>5% decrease	3/61 (4.9)	1/24 (4.2)	4/85 (4.7)	12/411 (2.9)	4/53 (7.5)	16/464 (3.4)
Uric Acid						
>50% increase	4/60 (6.7)	2/24 (8.3)	6/84(7.1)	16/407 (3.9)	4/53 (7.5)	20/460 (4.3)

For summaries of selected notable liver function test parameters (total bilirubin, SGOT/AST, and SGPT/ALT), 1 CKD patient and 6 non-CKD patients (all in the Val Mono group) had SGPT/ALT >3x the upper limit of the reference range.

A summary of patients with selected notable potassium values (>5.3, >5.5, or >6.0 mEq/L) at any time during the treatment period is provided by baseline eGFR category in table below. Potassium values >5.3 mEq/L and >5.5 mEq/L occurred in 29.4% and 28.2% of CKD patients, respectively, and in 4.7% and 2.6% of non-CKD patients, respectively. In CKD patients,

incidences of selected notable potassium values were higher in the Val AHY than the Val Mono group.

A total of 7 patients each in the CKD and non-CKD subgroups had potassium values >6.0 mEq/L (8.2% and 1.5%, respectively). Of these 14 patients, 3 were in Study A2302, 6 in Study K2302E1, and 5 in Study K2305. Four cases resolved while treatment continued, 4 cases resolved after treatment discontinuation, 1 sample was hemolyzed, and in 5 cases a repeat potassium value was not reported.

A summary by study is provided below.
In Study A2302, for 1 of the 3 patients with potassium >6.0 mEq/L, the high value was reported on the day of study discontinuation (discontinuation due to an SAE of hypertensive encephalopathy); the patient was a CKD patient. No potassium-related AEs were reported in Study A2302 for the other 2 patients (non-CKD patients).
In Study K2302E1, hyperkalemia was reported as an SAE in 2 CKD patients and as an AE in 3 CKD patients. For 1 non-CKD patient, a potassium value >6.0 mEq/L was noted by the investigator as probably due to sample hemolysis. Of the 3 patients with hyperkalemia AEs, 1 also had an SAE of synostosis and all 3 patients discontinued due to the hyperkalemia.
Of the 5 patients in Study K2305 with potassium value >6.0 mEq/L, 2 (1 CKD and 1 non-CKD) discontinued due to AEs of hyperkalemia, 1 non-CKD patient had an AE of hyperkalemia with no action taken and completed the study, and 2 non-CKD patients completed the study with no potassium–related AEs reported.

Table 15 - Number (%) of patients with selected notable potassium values at any time during treatment period by category of baseline eGFR (Safety set)

	Baseline eGFR < 90mL/min/1.73m^2			Baseline eGFR ≥ 90mL/min/1.73m^2		
Parameter Criterion	Val Mono N = 61 n/m (%)	Val AHY[1] N = 24 n/m (%)	All Val N = 85 n/m (%)	Val Mono N = 420 n/m (%)	Val AHY[1] N = 53 n/m (%)	All Val N = 473 n/m (%)
Potassium						
> 5.3 mEq/L	14/61 (23.0)	11/24 (45.8)	25/85 (29.4)	19/412 (4.6)	3/53 (5.7)	22/465 (4.7)
> 5.5 mEq/L	13/61 (21.3)	11/24 (45.8)	24/85 (28.2)	10/412 (2.4)	2/53 (3.8)	12/465 (2.6)
> 6.0 mEq/L	1/61 (1.6)	6/24 (25.0)	7/85 (8.2)	6/412 (1.5)	1/53 (1.9)	7/465 (1.5)

Assessor's comment:
Deviations in laboratory assessment were more common in patients with CKD with increases in serum potassium, creatinine, and BUN and decreases in eGFR seen more commonly than in non-CKD patients. These findings are consistent with the SmPC which states that hyperkalemia has been observed in children and adolescents aged 6 to 18 years with underlying chronic kidney disease. The SmPC states that renal function and serum potassium should be closely monitored in paediatric patients.

Vital signs / Orthostatic blood pressure changes
Orthostatic blood pressure change data were summarized for the safety population. Orthostatic blood pressure change was defined as a decrease of at least 20 mmHg in mean systolic blood pressure or a decrease of at least 10 mmHg in mean diastolic blood pressure when a patient moves from a sitting position to a standing position.
At baseline there were 6.1% of patients with orthostatic blood pressure changes, at endpoint there were 5.1% of patients and at any post-baseline visit, 31.2% of patients had orthostatic blood pressure changes.

The incidence of orthostatic blood pressure changes during the treatment period was similar for CKD and non-CKD patients.

Safety in special groups and situations
In addition to the subgroup analyses according to baseline eGFR category, the following additional subgroups were defined:

- Age groups: 6-11 (inclusive) years, 12-17 (inclusive) years at baseline
- Gender: Female, Male
- Region group: Europe, Rest of the world

Mean durations of exposure by subgroup were as follows:

- Age group: 321.4 days for 6-11 years and 305.5 days for 12-17 years
- Gender: 316.3 days for males and 305.0 days for females
- Region group: 282.0 days for Europe and 332.9 days for Rest of the world.

The incidences of AEs and SAEs were generally comparable across the subgroups evaluated, including the pattern and types of individual AEs/SAEs observed. As in the overall population, headache, cough, nasopharyngitis and pyrexia were the most frequent AEs across subgroups, with lower percentages reported in the summary by region for Europe than in the rest of world countries. Severity of AEs was also comparable across subgroups, and with most AEs of mild or moderate severity, as in the overall population.

The percentages of patients with clinically notable hematology and clinically or selected notable biochemistry values were comparable across subgroups.

Overall, there were no clinically meaningful differences among the subgroups evaluated, and no suggestion of a difference among subgroups that would suggest a vulnerability of a particular group to an AE.

3. Discussion on clinical aspects

For Diovan, additional long term safety data was requested when the paediatric indication was granted in 2010. The CHMP noted that lack of such safety data in the pediatric population included children with or without chronic kidney disease (CKD). The company committed to perform the long-term safety study CVAL489K2305 (referred to as Study K2305). In this study, 150 paediatric patients (6-17 years) were treated open label for 78 weeks.

Because the requirement was to include safety data from 90 paediatric CKD patients (eGFR <90 mL/min/1.73m^2) the company has submitted data from study K2305 together with pooled paediatric safety data from four studies in children. Taken together, this data base includes 85 CKD patients. Generally, the safety profile observed in Study K2305 was similar to the safety profile of the pooled population.

The subgroup of patients with CKD was more prone to report AEs. For example, more CKD patients had AEs in the category of hyperkalemia compared to non-CKD patients. Also, deviations in laboratory assessment were more common in patients with CKD; increases in serum potassium, creatinine, and BUN and decreases in eGFR were more commonly reported than in non-CKD patients. These findings are consistent with the SmPC which states that hyperkalemia has been observed in children and adolescents aged 6 to 18 years with underlying chronic kidney disease. The SmPC states that renal function and serum potassium should be closely monitored in paediatric patients.

From patients on combined treatment, higher incidences of adverse events were reported compared to patients receiving valsartan as monotherapy. The group on combined treatment included a greater percentage of CKD patients compared to the monotherapy group which may partly explain the difference between patients on mono-, and combined therapy.

As regards related AEs, the most frequently reported suspected related AEs were headache, dizziness and hyperkalemia which are included in the current SmPC.

The data submitted does not contain any apparent signs of safety issues associated with long-term treatment in this population. This is in accordance with the SmPC which mentions that no clinically relevant adverse impact in neurocognitive and developmental assessments were revealed after treatment with valsartan for up to one year in paediatric patients aged 6 to 16 years.

Efficacy was a secondary endpoint in the study. Clinically significant reductions in blood pressure were seen at each timepoint during the treatment period. The percentage of patients who achieved overall blood pressure control was slightly higher in the CKD population compared to the non-CKD population. In the majority of patients, urine albumin/creatinine ratio (UACR) either decreased or remained the same at study end compared to baseline. In the overall CKD population, mean UACR decreased and the reduction was sustained throughout the study.

The current SmPC contains comprehensive information on use of valsartan in paediatric patients in sections 4.2, 4.4, 4.5, 4.8, and 5.1. Among other things, the SmPC contains summaries of data from the controlled studies with valsartan in paediatric patients. Use in paediatric patients with eGFR <30 mL/min/1.73m^2 is not recommended and this category was excluded from participating in study K2305 and the other referenced studies. Study K2305 included hypertensive patients with CKD and the rapporteur supports the member states comments (see section VII) that information from study K2305 should be added to sections 4.8 and 5.1 of the SmPC.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- Overall conclusion

As presented in this submission, the long term safety data of valsartan in paediatric hypertensive patients aged 6-17 years shows that valsartan was generally well-tolerated in patients with or without underlying CKD. The benefit/risk balance for valsartan remains unchanged for the approved indication of hypertension in children aged 6 to 17 years with or without CKD.

The questions and comments raised by the rapporteur and by the member states during the procedure have been responded to satisfactorily. Addition of text in sections 4.8 and 5.1 of the SmPC are recommended. No PL changes are proposed.

- **Recommendation**

The following revisions of the SmPC are recommended:

Section 4.8, addition of text under header Hypertension (with bolded/italics) and deletions (with strike through)

The antihypertensive effect of valsartan has been evaluated in two randomised, double-blind clinical studies (each followed by an extension period or study) and one open-label study. These studies included 711 ~~561~~ paediatric patients from 6 to ***less than*** 18 years of age ***with and without chronic kidney disease (CKD), of which 560 patients received valsartan***. With the exception of isolated gastrointestinal disorders (***such as*** ~~like~~ abdominal pain, nausea, vomiting) and dizziness, no relevant differences in terms of type, frequency and severity of adverse reactions were identified between the safety profile for paediatric patients aged 6 to ***less than*** 18 years and that previously reported for adult patients.

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A pooled analysis of 560 paediatric hypertensive patients (aged 6-17 years) receiving either valsartan monotherapy [n=483] or combination antihypertensive therapy including valsartan [n=77] was conducted. Of the 560 patients, 85 (15.2%) had CKD (baseline GFR <90 mL/min/1.73m^2). Overall, 45 (8.0%) patients discontinued a study due to adverse events. Overall 111 (19.8%) patients experienced an adverse drug reaction (ADR), with headache (5.4%), dizziness (2.3%), and hyperkalemia (2.3%) being the most frequent. In patients with CKD, the most frequent ADRs were hyperkalaemia (12.9%), headache (7.1%), blood creatinine increased (5.9%), and hypotension (4.7%). In patients without CKD, the most frequent ADRs were headache (5.1%) and dizziness (2.7%). ADRs were observed more frequently in patients receiving valsartan in combination with other antihypertensive medications than valsartan alone.

Section 5.1, addition of the following text:

In a third, open label clinical study, involving 150 paediatric hypertensive patients 6 to 17 years of age, eligible patients (systolic BP ≥95th percentile for age, gender and height) received valsartan for 18 months to evaluate safety and tolerability. Out of the 150 patients participating in this study, 41 patients also received concomitant antihypertensive medication. Patients were dosed based on their weight categories for starting and maintenance doses. Patients weighing ≥18 to < 35 kg, ≥35 to < 80 kg and ≥ 80 to < 160 kg received 40 mg, 80 mg and 160 mg and the doses were titrated to 80 mg, 160 mg and 320 mg respectively after one week. One half of the patients enrolled (50.0%, n=75) had CKD with 29.3% (44) of patients having CKD Stage 2 (GFR 60 – 89 mL/min/1.73m2) or Stage 3 (GFR 30-59 mL/min/1.73m2). Mean reductions in systolic blood pressure were 14.9 mmHg in all patients (baseline 133.5 mmHg), 18.4 mmHg in patients with CKD (baseline 131.9 mmHg) and 11.5 mmHg in patients without CKD (baseline 135.1 mmHg). The percentage of patients who achieved overall BP control (both systolic and diastolic BP <95th percentile) was slightly higher in the CKD group (79.5%) compared to the non-CKD group (72.2%).

Type IB variation to be requested from the MAH by 7th of August 2017. Type IB variation to be requested from other MAHs within 60 days of the publication of the public assessment report.