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

Crestor 5 mg, 10 mg, 20 mg, and 40 mg film-coated tablets

(rosuvastatin)

NL/W/0011/pdWS/002

Marketing Authorisation Holder: Astra Zeneca

Rapporteur:	NL
Finalisation procedure (day 120):	30 May 2018

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Crestor
INN (or common name) of the active substance(s):	Rosuvastatin
MAH:	Astra Zeneca
Currently approved Indication(s)	Treatment of hypercholesterolemia Prevention of cardiovascular events
Pharmaco-therapeutic group (ATC Code):	C10AA07
Pharmaceutical form(s) and strength(s):	Film-coated tablets, 5 mg Film-coated tablets, 10 mg Film-coated tablets, 20 mg Film-coated tablets, 40 mg

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ApoA-1	Apolipoprotein A1
ApoB	Apolipoprotein B
AST	Aspartate Aminotransferase
CI	Confidence Interval
CK	Creatine Kinase
FAS	Full Analysis Set
GFR	Glomerular Filtration Rate
HbA1c	Glycosylated Haemoglobin
HDL-C	High Density Lipoprotein Cholesterol
HeFH	Heterozygous Familial Hypercholesterolemia
HoFH	Homozygous Familial Hypercholesterolemia
LDL-C	Low Density Lipoprotein Cholesterol
MAH	Marketing Authorisation Holder
PdWS	Paediatric Worksharing
PK	Pharmacokinetics
PL	Package leaflet
QD	Quaque Die
SmPC	Summary of Product Characteristics
TC	Total Cholesterol
TG	Triglyceride
UACR	Urine Albumin-to-Creatine Ratio
ULN	Upper Limit of Normal

I. EXECUTIVE SUMMARY

SmPC changes are proposed in section 5.1.

II. RECOMMENDATION

The results of the submitted paediatric study do not influence the benefit risk for rosuvastatin. The SmPC should be updated to reflect the results of the extension study and the single patient that received the 40 mg dose.

III. INTRODUCTION

On 29 May 2017, the MAH submitted a completed paediatric study for Crestor, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

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

IV. SCIENTIFIC DISCUSSION

IV.1 Clinical aspects

IV.1.1 Introduction

The MAH submitted a final report for:

- **D356NC00001 *HYDRA LTE***: An open-label long-term extension to the randomized, double-blind, placebo-controlled, multi-centre, crossover study of rosuvastatin in children and adolescents (aged 6 to <18 years) with Homozygous Familial Hypercholesterolemia (HoFH).

Earlier approval of an indication for paediatric patients from six years of age was based on the CHARON and PLUTO studies. In the CHARON and PLUTO studies (paediatric patients with HeFH), a decrease in LDL-C of 38% was observed following three months of treatment with rosuvastatin 5 mg, and, over the dose range of 5 mg to 20 mg following 12 months of treatment, decreases in LDL-C ranging from 44% to 46% were observed. In Study 54, a study in both adults and paediatric patients with HoFH in which patients received a forced titration of rosuvastatin from 20 mg to 40 mg to 80 mg at six week intervals, the mean LDL-C reduction from baseline following 18 weeks of treatment was 21%, most of the decrease had occurred by Week 6 on rosuvastatin 20

mg, and incremental benefit was observed with increased dose above 40 mg/day (Marais et al., 2008[1]).

The current study submission is an extension of the placebo controlled crossover (two times six weeks) HYDRA study in HoFH patients aged 6 to 17 years, for which an indication for the HoFH population was approved.

IV.1.2 Clinical study D356NC00001 *HYDRA LTE*

Methods

Objectives

- The safety objective of the study was to assess the long-term safety and tolerability of rosuvastatin 20 mg in paediatric patients with HoFH.
- The efficacy objective of the study was to assess the longitudinal profile of rosuvastatin 20 mg on lipid parameters (LDL-C, HDL-C, TC, TG, non-HDL-C, LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, ApoA-1, and ApoB/ApoA-1).
- The pharmacokinetic objective of the study was to characterize the trough plasma exposure of rosuvastatin in pediatric patients with HoFH who were up-titrated to a daily dose of rosuvastatin 40 mg.

Study design

This HYDRA long term extension (LTE) study was an open-label, long-term extension to the randomized, double-blind, cross-over study of rosuvastatin 20 mg once daily (QD) versus placebo QD in children and adolescents (aged from 6 to <18 years) with HoFH (HYDRA). In the parent HYDRA study, patients were randomized 1:1 to one of two treatment sequences in the cross-over phase, where Sequence A consisted of six weeks of treatment with rosuvastatin 20 mg QD followed by six weeks of matching placebo QD and Sequence B consisted of six weeks of matching placebo QD followed by six weeks of treatment with rosuvastatin 20 mg QD. The randomized, cross-over phase was followed by a 12 week efficacy maintenance phase, during which all patients received rosuvastatin 20 mg QD. In this HYDRA LTE study, all patients received rosuvastatin 20 mg and could be up-titrated to 40 mg as described below.

Investigators were permitted to titrate the dose of rosuvastatin from 20 to 40 mg per day if they felt it was warranted to more aggressively treat patients' elevated LDL-C levels. This up-titration was not permitted in Asian patients because of the increased rosuvastatin plasma concentrations that would be anticipated in this patient population. (Per local clinical study protocol Amendment 1.1, the up-titration of rosuvastatin 20 mg to 40 mg QD and subsequent PK sampling was not permitted in Israel.)

The study aimed to enrol approximately 20 patients who had completed the HYDRA study, including those who had reached their 18th birthday during that study.

[1] Marais AD, Raal JR, Stein EA, Rader DJ, Blasetto J, Palmer M, Wilpshaar W. A dose-titration and comparative study of rosuvastatin and atorvastatin in patients with homozygous familial hypercholesterolaemia. Volume 197, Issue 1, March 2008, Pages 400-406.

Patients qualified for the study by completing the HYDRA study and by meeting all inclusion and none of the exclusion criteria at screening (last visit in HYDRA/Visit 1 in HYDRA LTE). In the HYDRA study, patients were permitted to continue stable treatment with apheresis and/or ezetimibe throughout that study, but no other lipid-lowering therapy was allowed. In this HYDRA LTE study, investigators were allowed to incorporate apheresis, ezetimibe, and/or bile-acid sequestrants as concomitant therapy, but no other concomitant lipid-lowering therapy (e.g., fibrates, niacin, or statins other than the rosuvastatin provided) was permitted.

Since there is limited exposure data for rosuvastatin doses above 20 mg in paediatric patients, study patients who were up-titrated to rosuvastatin 40 mg were asked to return for an additional study visit six weeks after initiating the 40 mg rosuvastatin dose in order to carefully monitor the safety and tolerability of this dosage. At that visit, adverse event (AE) and safety laboratory assessments were made, and a blood sample for analysis of the trough plasma exposure of rosuvastatin was taken. If the 40 mg dose was well tolerated at that visit, the normal study visit schedule at 12 week intervals was to resume, with a second blood sample for analysis of the trough plasma exposure of rosuvastatin collected at the next study visit.

The final visit of the HYDRA study constituted the first visit of the HYDRA LTE study (12 weeks from end of placebo for patients in Sequence A and 18 weeks from end of placebo in Sequence B). Thereafter, blood samples were drawn at the end of each 12 week period until the LTE study concluded. For patients who were undergoing apheresis, it was optimal to have blood drawn at least seven days following the last apheresis. Because of the rapid changes that occur in LDL-C levels following apheresis, it was very important to ensure that blood samples were scheduled to be drawn the same number of days following the last apheresis and at the same time of the day in relation to the last apheresis. Blood samples were to be drawn in association with the apheresis and were to be obtained before the apheresis procedure. Processes were put in place at each site where patients underwent apheresis to enable verification of start/stop dates and times of apheresis procedures against source documentation from their respective dialysis units.

Figure 1 shows the design of the study and the sequence of treatment periods.

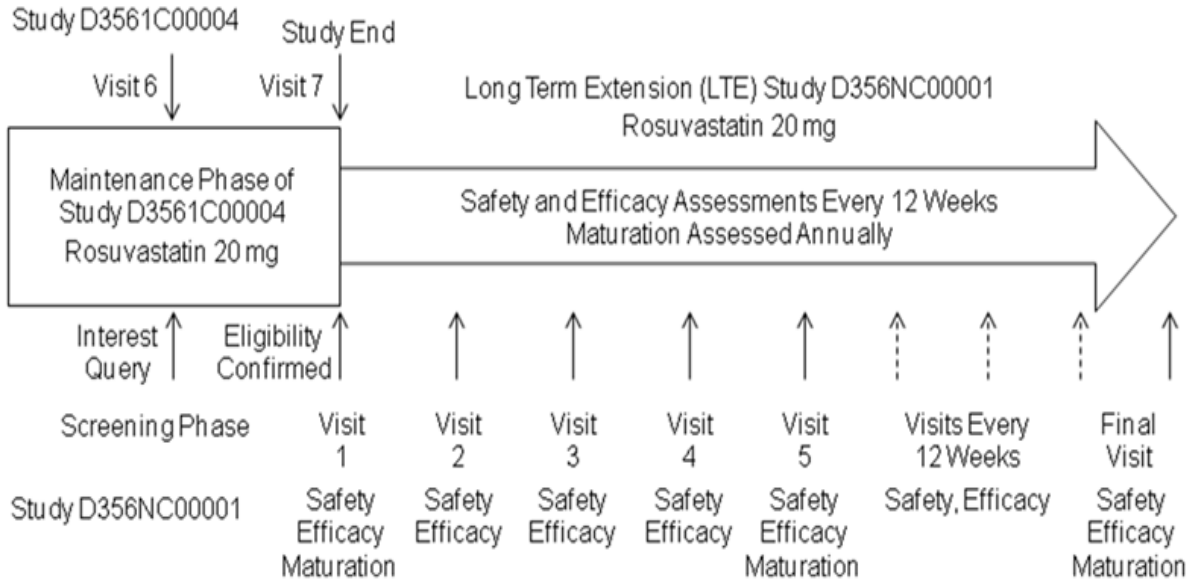

Figure 1. Flow chart of study design

Note: At Visit 6 of the HYDRA study, the patients were asked if they wanted to enrol in the LTE study. Once the parent/both parents or guardian, and patient if applicable, had signed the informed consent form for the LTE study, then the patient was screened for eligibility for the HYDRA LTE study. Screening could occur any time after Visit 6 of HYDRA prior to enrolment in the HYDRA LTE study.

Study population/Sample size

For inclusion in the study, patients had to fulfil all of the following criteria:

- Written informed consent from a parent/both parents or guardian and statement of assent from the child or adolescent.
- At the onset of the HYDRA:
    - Documentation of genetic testing confirming two mutated alleles of either the LDL receptor gene locus, ApoB or PCSK9; and/or
    - Documented untreated LDL-C >500 mg/dL (12.9 mmol/L) and TG <400 mg/dL (4.5 mmol/L) and at least one of the following criteria:
        - Tendinous and/or cutaneous xanthoma prior to 10 years of age; or
        - Documentation of HeFH in both parents by:
            - genetic and/or
            - clinical criteria
- Negative pregnancy test. Male patients should have refrained from fathering a child (including sperm donation) during the study and for three months following the last dose.
- Were taking study drug at the end of the HYDRA study and were willing to follow all study procedures including adherence to dietary guidelines, study visits, fasting blood draws, and compliance with study treatment regimens.

The most important exclusion criteria from the study were as follows:

- History of statin-induced myopathy or serious hypersensitivity reaction to other HMG-CoA reductase inhibitors (statins), including rosuvastatin, at Visit 1 of the HYDRA

study. Also, definite or suspected personal history or family history of clinically significant adverse drug reactions, or hypersensitivity to drugs with a similar chemical structure to rosuvastatin as well as other statins.

- Fasting serum glucose of >180 mg/dL (9.99 mmol/L) or glycosylated haemoglobin (HbA1c) >9% during the HYDRA study or patients with a history of diabetic ketoacidosis within the past year.
- Uncontrolled hypothyroidism defined as thyroid stimulating hormone >1.5 times the upper limit of normal (ULN) at any time during the HYDRA study.
- Evidence of active liver disease or hepatic dysfunction (except a confirmed diagnosis of Gilbert's disease) as defined as non-transient alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations ≥three times the ULN or non-transient total bilirubin ≥two times the ULN during the HYDRA study. Treatment in the previous three months with any drug known to have a well-defined potential for hepatotoxicity (e.g. halothane).
- Serum creatine kinase (CK) ≥three times ULN (unless transient and/or explained by exercise) during the HYDRA study. Estimated glomerular filtration rate (GFR) by Schwartz formula <50 mL/min at Visit 1 of the HYDRA study. A non-transient finding of ≥2+ proteinuria on urine dipstick during the HYDRA study.
- Stage 2 hypertension (non-transient systolic and/or diastolic blood pressure greater than 5 mmHg above the 99th percentile for age, gender, and height) during the HYDRA study.
- History of solid organ transplantation reported at any time.
- At the discretion of the investigator, any new and clinically significant abnormalities in medical history, clinical chemistry, haematology, or urinalysis results.
- History or presence of gastrointestinal, hepatic, or renal disease or other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.
- Patients weighing <20 kg (44 lb).
- Pregnancy or currently lactating.

Treatments

In this HYDRA LTE study, all patients received rosuvastatin 20 mg and could be up-titrated to 40 mg. Investigators were permitted to titrate the dose of rosuvastatin from 20 mg to 40 mg per day if they felt it was warranted to more aggressively treat patients' elevated LDL-C levels. This up-titration was not permitted in Asian patients because of the increased rosuvastatin plasma concentrations that would be anticipated in this patient population.

Outcomes/endpoints

The concentration of fasting LDL-C was determined for all relevant visits by the Friedewald Equation. In the HYDRA LTE study, study assessments were performed at 12 week intervals. Due to the cross-over design in the parent HYDRA study, the first visit of the HYDRA LTE study occurred 12 weeks from end of placebo for patients in Sequence A and 18 weeks from end of placebo in Sequence B. Because the analyses of lipid parameters were conducted for the total duration of the HYDRA and HYDRA LTE studies (from the end of the placebo period in the HYDRA study to the end of the HYDRA LTE study), data during the HYDRA LTE study for patients randomized to Sequence A are summarized at 12, 24, 36, 48, 60, 72, and 84 weeks from the end of

placebo and data for patients randomized to Sequence B are summarized at 18, 30, 42, 54, 66, 78, and 90 weeks from the end of placebo.

Statistical Methods
Each efficacy outcome variable was assessed over time by graphical representation of the mean with 95% confidence interval (CI) as well as individual patient profiles from the end of the placebo period in the HYDRA study to later time points based on the full analysis set (FAS).

A longitudinal analysis from the end of the placebo period in the HYDRA study was performed with a mixed-effects model repeated measures analysis including time or visits since the end of the placebo period as a fixed effect and patient as a random effect. The analysis was based on the FAS. The lipid variable was included in the model on the log scale and was back-transformed and presented as the percent change from the end of the placebo period to each later time point with 95% CI. The estimate of the percent change from end of placebo (δ) of the lipid parameter in logarithm was transformed back into the relative difference in percent:

$$Rel\_D\_Pct = [\exp(\delta) - 1] \times 100$$

Results
Recruitment/ Number analysed
A total of nine patients who completed the HYDRA study (four patients randomized to Sequence A [rosuvastatin 20 mg QD followed by placebo QD] and five patients randomized to Sequence B [placebo QD followed by rosuvastatin 20 mg QD] in the cross-over phase) enrolled in the HYDRA LTE study. Five patients were prematurely withdrawn from the LTE study: two patients withdrew consent (subject decision) and three patients withdrew so that the investigator could begin a prohibited concomitant medication.
Of the nine patients enrolled in the LTE study, all patients received at least one dose of study drug and were, therefore, included in both the FAS and Safety analysis set.

Baseline data
Patients ranged from 7 to 15 years of age (at HYDRA LTE Visit 1) and most were white (six of nine patients). Four patients were treated with apheresis throughout the study and seven were treated with ezetimibe during the study (four patients were taking ezetimibe at study entry and three patients added ezetimibe after the beginning of the study). The demographic and key baseline characteristics were generally balanced across the HYDRA treatment sequences.

Pharmacokinetic results
The pharmacokinetic results of the 20 mg dose-group are in line with paediatric data reported in current SmPC.

Only one patient was up-titrated to rosuvastatin 40 mg per day on Day 253 relative to first dose in the HYDRA cross-over phase. The trough PK plasma samples of this patient were registered to have been collected within a time interval of approximately 28 hours after the last dose. Rosuvastatin trough concentrations were 9.00 ng/mL and 7.14 ng/mL on Day 292 and Day 376, respectively. This patient's trough levels on

rosuvastatin 20 mg during the previous HYDRA study were 2.70 ng/mL and 2.82 ng/mL The trough concentrations from this single patient on rosuvastatin 40 mg are displayed along with the trough concentrations on rosuvastatin 20 mg collected in the previously submitted HYDRA study (n=13) in figure 2.

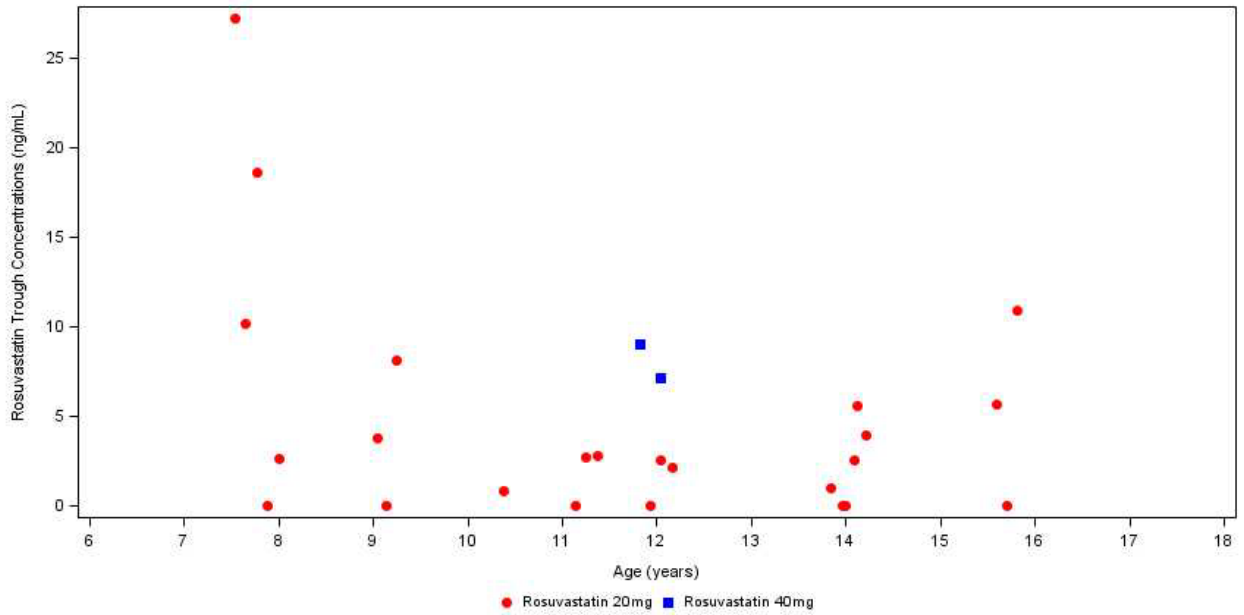

Figure 2. Patient profile of rosuvastatin trough concentrations (ng/mL) during study D356NC00001, over time (FAS)

The pharmacokinetic listing showed three patients, which were up-titrated to 40 mg and had PK samples taken. Initially it was not clear why data from the other two subjects were not reported. Also it was not clear why the listing mentions a 10 year-old subject while the same subject corresponds to a 12 year-old in figure 2. In response, the MAH clarified the inconsistency between listing and a submitted figure with respect to the age of the subject and to sufficiently explained why data from the other two subjects were not reported

Based on the final data of one subject on the 40 mg dose level no conclusions with respect to the pharmacokinetics can de drawn. The pharmacokinetic results of the 20 mg dose group are in line with paediatric data reported in current SmPC. Therefore there is no need to update the SmPC section 5.2.

Efficacy results

In the HYDRA study, the primary efficacy endpoint was LDL-C. The mean reductions in LDL-C at 6, 12, and 18 weeks from the end of placebo were -20.0% (n=13), -19.3% (n=11), and -16.5% (n=5), respectively.

As shown in figure 3, the mean LDL levels at the beginning of the HYDRA LTE study were maintained or diminished across visits throughout the study. At Visit 1 of the HYDRA LTE study, the mean reduction in LDL-C was -21.0% (n=7). The reductions in LDL-C fluctuated over the subsequent visits of the HYDRA LTE study (table 1).

As shown in figure 4, LDL-C levels in individual patients were generally maintained during the LTE study.

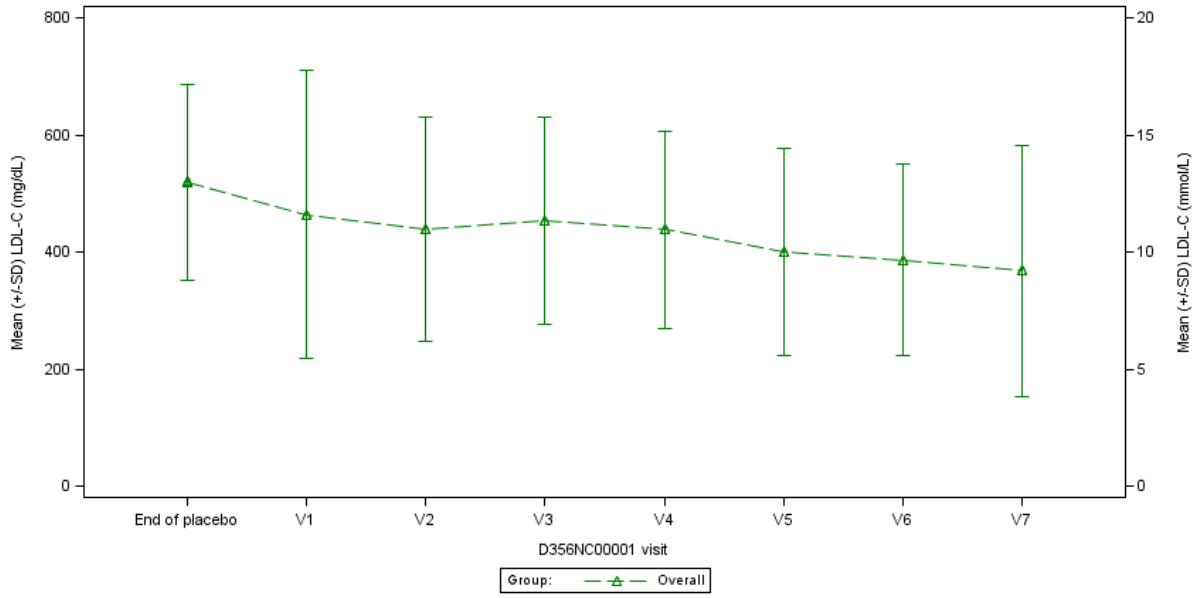

Figure 3. LDL-C from the end of the placebo period through the end of the HYDRA LTE study, mean (±SD) over time (FAS)

Table 1. Percent change in LDL-C from the end of the placebo period in HYDRA to each study visit in the HYDRA LTE study (FAS) *A mixed effects model repeated measures analysis, including time since the end of the placebo period as a fixed effect and patient as a random effect, was performed on log scale LDL-C.*

		% change from end of the placebo period[a]	
Time point	**n**	**Estimate**	**95% CI**
Visit 1	7	-21.0	(-32.1, -8.0)
Visit 2	9	-18.6	(-28.4, -7.4)
Visit 3	9	-14.7	(-25.2, -2.8)
Visit 4	8	-12.1	(-23.8, 1.4)
Visit 5	8	-21.3	(-33.7, -6.6)
Visit 6	7	-20.5	(-33.6, -4.8)
Visit 7	4	-12.4	(-28.2, 7.0)

[a] The percent change from end of placebo estimate and 95% CI are presented after transformation to the original scale: relative difference (%) estimate = [exp(treatment difference in log scale) - 1] × 100.

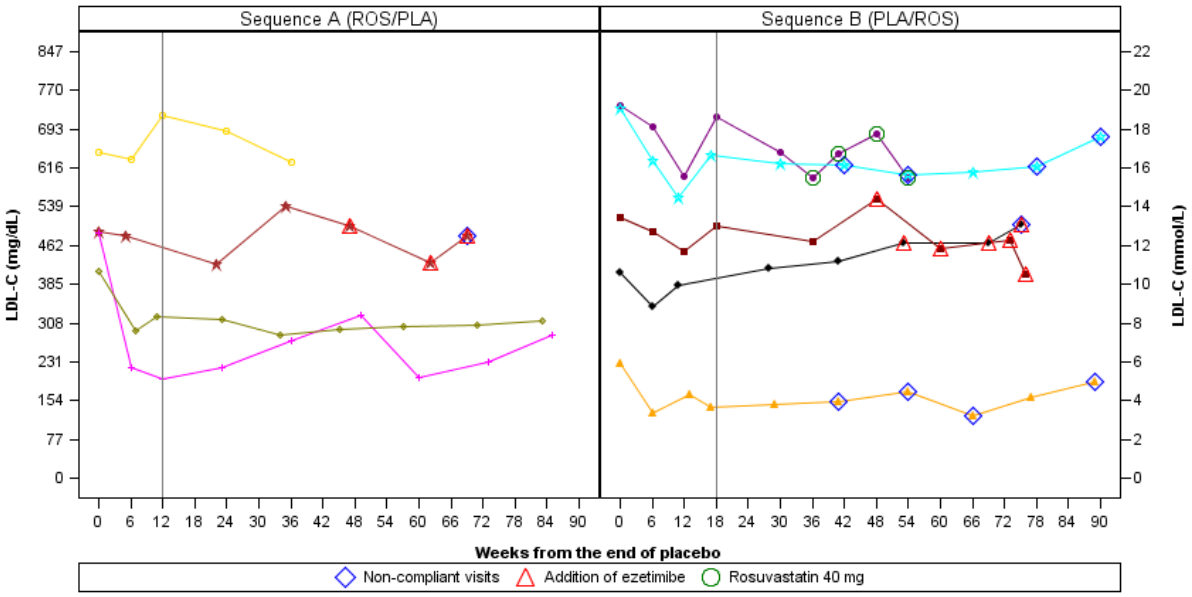

Figure 4. **Patient profile of LDL-C from end of placebo period through end of the HYDRA LTE study (FAS)**
Sequence A: rosuvastatin 20 mg QD followed by placebo QD.
Sequence B: placebo QD followed by rosuvastatin 20 mg QD.
Reference lines showing start of the HYDRA LTE study.
PLA placebo; ROS rosuvastatin.

Secondary efficacy endpoints

In the HYDRA study, the secondary efficacy endpoints were TC, non-HDL-C, and ApoB. These results of the analysis of these lipid parameters for the HYDRA LTE study are described below.

- *Total cholesterol*
  In the HYDRA study, the mean reductions in total cholesterol (TC) at 6, 12, and 18 weeks from the end of placebo were -18.0% (n=13), -16.9% (n=11), and -14.4% (n=5), respectively.
  The mean TC levels at the beginning of the HYDRA LTE study were maintained or diminished across visits throughout the study. At Visit 1 of the HYDRA LTE study, the mean reduction in TC was -19.4% (n=7). The reductions in TC fluctuated over the subsequent visits of the HYDRA LTE study (-11.8% to -19.9%). TC levels in individual patients were generally maintained during the LTE study.
- *Non-HDL-C*
  In the HYDRA study, the reductions in non-HDL-C at 6, 12, and 18 weeks from the end of placebo were -20.9% (n=13), -19.5% (n=11), and -15.4% (n=5), respectively.
  The mean non-HDL-C levels at the beginning of the HYDRA LTE study were maintained or diminished across visits throughout the study. At Visit 1 of the HYDRA LTE study, the mean reduction in non-HDL-C was -21.7% (n=7). The reductions in non-HDL-C fluctuated over the total duration of the HYDRA LTE study (-13.2% to -22.1%).
- *ApoB*
  In the HYDRA study, the reductions in ApoB at 6, 12, and 18 weeks from the end of placebo were -16.4% (n=13), -14.4% (n=11), and -19.0% (n=5), respectively.

The mean ApoB levels at the beginning of the HYDRA LTE study were maintained or diminished across visits throughout the study. At Visit 1 of the HYDRA LTE study, the mean reduction in ApoB was -20.5% (n=7). The reductions in ApoB fluctuated over the subsequent visits of the HYDRA LTE study (-9.5% to -19.2%).

Other lipid parameters

Other lipid parameters assessed in this study included HDL-C, TG, LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, ApoA-1, and ApoB/ApoA-1. Generally, each lipid parameter fluctuated over the subsequent visits of the HYDRA LTE study. And the levels in individual patients showed considerable variability during the LTE study.

- *HDL-C*
  At Visit 1 of the HYDRA LTE study, the mean increase in HDL-C was 12.3% (n=7). The increases in HDL-C were 3.8% to 19.0% during the study.
- *TG*
  At Visit 1 of the HYDRA LTE study, the mean reduction in TG was -17.3% (n=7). The reductions in TG were -16.2% to -28.5% during the study.
- *LDL-C/HDL-C*
  At Visit 1 of the HYDRA LTE study, the mean reduction in LDL-C/HDL-C was -32.4% (n=7). The reductions in LDL-C/HDL-C were -16.8% to -31.5% during the study.
- *TC/HDL-C*
  At Visit 1 of the HYDRA LTE study, the mean reduction in TC/HDL-C was -30.6% (n=7). The reductions in TC/HDL-C were -15.6% to -29.4% during the study.
- *Non-HDL-C/HDL-C*
  At Visit 1 of the HYDRA LTE study, the mean reduction in non-HDL-C/HDL-C was -32.9% (n=7). The reductions in non-HDL-C/HDL-C were -17.6% to -31.8% during the study.
- *ApoA-1*
  At Visit 1 of the HYDRA LTE study, the mean increase in ApoA-1 was 8.0% (n=7). The increases in ApoA-1 levels were 1.0% to 10.7% during the study.
- *ApoB/ApoA-1*
  At Visit 1 of the HYDRA LTE study, the mean decrease in ApoB/ApoA-1 was -23.3% (n=7). The reductions in ApoB/ApoA-1 levels were -14.7% to -26.0%.

Safety results

- *Exposure*
  For the nine patients enrolled in the LTE study, the mean overall exposure for rosuvastatin from the beginning of the cross-over phase of the HYDRA study to the end of the HYDRA LTE study was 529.8 days (approximately 1.5 years).
  The mean duration of exposure to rosuvastatin 20 mg was 42.3 and 78.6 days at the end of the cross-over and maintenance phases, respectively, during the HYDRA study and 390.6 days at the end of the HYDRA LTE study. One patient was up-titrated to rosuvastatin 40 mg per day starting on Day 253 (relative to first dose in the HYDRA cross-over phase) through the end of the LTE study, for a total exposure of 165 days.
- *Adverse events*
  A total of five of nine patients (55.6%) experienced ten treatment-emergent AEs: four patients experienced nine treatment-emergent AEs during treatment with

rosuvastatin 20 mg and one patient experienced one treatment-emergent AE during treatment with rosuvastatin 40 mg. The only treatment-emergent AE occurring in more than one patient was nasopharyngitis.

During treatment with rosuvastatin 20 mg, one patient experienced a total of five treatment-emergent AEs (otitis externa, attention deficit/hyperactivity disorder, ligament sprain, nasopharyngitis, and dysuria), one patient experienced two treatment-emergent AEs (upper respiratory infection and proteinuria) which overlapped in time, and one patient each experienced single treatment-emergent AEs of dysmenorrhea and chest discomfort.

During treatment with rosuvastatin 40 mg, one patient experienced a treatment-emergent AE of nasopharyngitis.

- *Adverse events of special interest*
  There were no hepatic events or skeletal muscle events during the HYDRA LTE study. There was one renal treatment-emergent AE (transient +1 proteinuria) that was considered by the investigator to be not related to rosuvastatin. See also section laboratory values below.
- *Treatment related adverse events*
  There were no treatment-emergent AEs assessed by the investigator to be related to study drug during the HYDRA LTE study.
- *Serious adverse events and deaths*
  There were no treatment-emergent SAEs reported during the HYDRA LTE study. One patient (rosuvastatin 20 mg) experienced a treatment-emergent AE of moderate intensity (otitis externa). All other treatment-emergent AEs reported for patients taking rosuvastatin during the HYDRA LTE study were of mild intensity.
- *Discontinuations due to adverse events*
  There were no treatment-emergent AEs that led to discontinuation of study drug during the HYDRA LTE study.
- *Laboratory values*
  - *Hepatic biochemistry*
    One patient had a liver function value (ALT) above 3x ULN while taking rosuvastatin 40 mg. There were no patients with more than one elevation in liver function above 3×ULN occurring sequentially. No patients had AST ≥3x ULN or total bilirubin ≥2x ULN at any time during the study. There were no patients who had signs and symptoms of liver injury, liver risk factors and life style events, or liver diagnostic investigations reported.
  - *Skeletal muscle biochemistry*
    One patient had several CK values above the ULN during the study. The values were not considered to be of clinical importance. This case is briefly described below:

    A 13-year-old white male, had normal CK values of 288 and 192 U/L (normal range 25 to 300 U/L), respectively, at the screening and baseline visits of the HYDRA study. At Week 6, following treatment with rosuvastatin 20 mg, the patient's CK value was elevated at 371 U/L (1.2x ULN). The patient's CK values returned to within normal limits at the Week 12 and 18 visits (283 and 266 U/L, respectively) but was again elevated at 588 U/L (1.96x ULN) at Week 24. During the HYDRA LTE study, the patient's CK values continued to fluctuate with elevations observed at Week 36 (467 U/L [1.6x ULN]), Week 60 (936 U/L [3.1x ULN]), and at Week 96/final visit (545 U/L [1.8x ULN]).

There were no patients with CK increases >10x ULN. There were no cases of rhabdomyolysis or myopathy.

- *Renal biochemistry*
  No patients had serum creatinine values or estimated GFR outside of the normal reference range at any time during the study.
  One patient had a Urine Albumin-to-Creatine Ratio (UACR) >30 mg/g and increase >50% from baseline during the HYDRA LTE study. Full narratives for this patient are provided below.
  The laboratory abnormality of concern is a UACR increase by >50% to >30 mg/g. The patient had UACR values within normal range of 8 mg/g (normal range 0 to 14 mg/g) at Visit 2 (Day 82, 15 September 2015), 13 mg/g at Visit 3 (Day 159, 1 December 2015), and 9 mg/g at Visit 4 (Day 236, 16 February 2016). At Visit 5 (Day 320, 10 May 2016), the patient had an elevated UACR of 48 mg/g. Local testing a week later on Day 327 (17 May 2016) revealed that the UACR had returned to normal (12 mg/g). The patient's UACR was minimally elevated at Visit 6 (15 mg/g, Day 418, 16 August 2016) and was elevated but <30 mg/g at the Final Visit (28 mg/g, Day 502, 8 November 2016). Estimated GFR remained normal throughout the study (190, 195, 207, 182, 173, and 207 mL/min/1.73 m^2 [normal range >50 mL/min/1.73m^2] at Visits 2, 3, 4, 5, 6 and 7, respectively). Serum creatinine remained stable and normal throughout the study. The investigator did not consider the transient elevation of UACR above 30 mg/g to be an AE.
- *HbA1c and fasting glucose*
  There were no notable trends observed for HbA1c or fasting glucose during the HYDRA LTE study. A categorical shift in HbA1c (categories <5.7%, 5.7% to <6.5%, ≥6.5%) occurred in one patient (shift down 1 level from 5.7% to <6.5% to <5.7%), and a categorical shift in glucose (categories <65 mg/dL, 65 to <100 mg/dL, 100 to <126 mg/dL, and ≥126 mg/dL) occurred in one patient (shift up one level from 65 to <100 mg/dL to 100 to <126 mg/dL).

- *Vital signs*
  - *Height and weight*
    Small mean increases in height and weight were observed over time in the HYDRA LTE study.
  - *Sexual maturation*
    Shifts upward in Tanner staging were observed in two patients during the HYDRA LTE study.

IV.1.3 Discussion on clinical aspects

The MAH provided the data of the HYDRA long term extension study, which included data up to 90 weeks (weeks from the end of placebo in HYDRA) of treatment with rosuvastatin 20 mg in children aged 7-15 years of age. Inclusion criteria were generally similar to the HYDRA study and acceptable. From the 13 patients who completed the HYDRA controlled phase, nine entered this extension phase. Four patients completed to the last visit, resulting in a mean exposure for the nine patients of approximately 1.5 years from the start of treatment. During the study, fluctuations in effect on LDL-C could be observed in a range of -12% to -21.3%, although LDL-C levels were generally maintained when individual LDL-C levels over time are observed. However, interpretation of the data is complicated by non-compliance visits, and addition of

ezetimibe for some of the patients to the treatment strategy. Comparable findings as for LDL-C could also be observed for the other parameters of the lipid spectrum. For the one patient that was reported to be up-titrated to the 40 mg dose, no clear additional LDL-C reduction could be observed. The current dose recommendation in the SmPC indicates that paediatric patients should not be treated with the 40 mg dose, which is supported. Based on the data of this single subject on the 40mg dose level no conclusions with respect to the PK can de drawn.

A total of five of nine patients (55.6%) experienced ten treatment-emergent AEs. These types of AEs have been previously observed in the paediatric population. One patient had fluctuating CK levels during the study, and temporary proteinuria. Further, one case of ALT liver enzyme elevation on 40 mg dose was found. No patients discontinuing due to AEs, and no abnormal trends for weight, height and sexual maturations were observed. The safety profile can be considered acceptable and can be considered in line with previous safety findings in the paediatric population.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

V.1 Overall conclusion

The results of the submitted paediatric study do not influence the benefit risk for rosuvastatin. Data concerning experience of treatment in the paediatric population should be included in SmPC section 5.1 as follows (additions in bold):

Rosuvastatin was studied in a randomised, double-blind, placebo-controlled, multicenter, cross-over study with 20 mg once daily versus placebo in 14 children and adolescents (aged from 6 to 17 years) with homozygous familial hypercholesterolaemia. The study included an active 4-week dietary lead-in phase during which patients were treated with rosuvastatin 10 mg, a cross-over phase that consisted of a 6-week treatment period with rosuvastatin 20 mg preceded or followed by a 6-week placebo treatment period, and a 12-week maintenance phase during which all patients were treated with rosuvastatin 20 mg. Patients who entered the study on ezetimibe or apheresis therapy continued the treatment throughout the entire study.

A statistically significant (p=0.005) reduction in LDL-C (22.3%, 85.4 mg/dL or 2.2 mmol/L) was observed following 6 weeks of treatment with rosuvastatin 20 mg versus placebo. Statistically significant reductions in Total-C (20.1%, p=0.003), non-HDL-C (22.9%, p=0.003), and ApoB (17.1%, p=0.024) were observed. Reductions were also seen in TG, LDL-C/HDL-C, Total-C/HDL-C, non-HDL-C/HDL-C, and ApoB/ApoA-1 following 6 weeks of treatment with rosuvastatin 20 mg versus placebo. The reduction in LDL-C after 6 weeks of treatment with rosuvastatin 20 mg following 6 weeks of treatment with placebo was maintained over 12 weeks of continuous therapy.

One patient had a further reduction in LDL-C (8.0%), Total -C (6.7%) and non-HDL-C (7.4%) following 6 weeks of treatment with 40 mg after up-titration.

During an extended open-label treatment in 9 of these patients with 20 mg rosuvastatin for up to 90 weeks the LDL-C reduction was maintained in the range of -12.1% to -21.3%.

There is no need to update the pharmacokinetic section 5.2 of the SmPC, as the submitted PK data are too limited to draw any conclusions on the 40 mg dose level in children..

V.2 Recommendation

The MAH is requested - in line with the guidance on Art. 46 Paediatric worksharing - to submit a type IB variation to update the product information in line with the PdWS conclusion (see above).