PCSK9 ODYSSEY PROGRAM - Clinical Sciences & Operations

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To: **DFI14223 study Investigators**

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SITE MEMO #6 – DFI14223: Summary of Study Results and Synopsis of the Clinical Study Report (CSR)

Dear site Investigators,

We are pleased to share with you a summary of the results of the DFI14223 study: An 8-Week Open-Label, Sequential, Repeated Dose-Finding Study to Evaluate the Efficacy and Safety of Alirocumab in Children and Adolescents with Heterozygous Familial Hypercholesterolemia Followed by an Extension Phase.

In summary, this study which enrolled 42 heterozygous familial hypercholesterolemia (heFH) patients from 8 to 17 years of age into 1 of 4 cohorts demonstrated that alirocumab significantly reduced LDL-C in this pediatric population, similar to what was observed in the adult population. Patients in all cohorts were stratified according to body weight (BW), either <50 kg and ≥50 kg. Lower doses evaluating the Q2W and Q4W regimens were tested in Cohorts 1 and 3, respectively and higher doses evaluating the Q2W and Q4W regimens were tested in Cohorts 2 and 4, respectively.

Overall, the primary efficacy endpoint (as measured by the percent change from baseline in LDL-C at Week 8) showed clinically meaningful reduction in LDL-C with the higher doses evaluating the Q2W and Q4W regimens: The least square (LS) mean percent change from baseline of -46.1% in Cohort 2 (40 or 75 mg Q2W) and LS mean percent change from baseline of -44.5% in Cohort 4 (150 or 300 mg Q4W). The highest effect on LDL-C reduction was observed in Cohort 2 (40 mg Q2W for BW <50 kg and 75 mg Q2W for BW ≥50 kg) and in Cohort 4 (150 mg Q4W for BW <50 kg and 300 mg Q4W for BW ≥50 kg). Substantial reductions from baseline to Week 8 were consistently observed in both BW categories for both Cohorts 2 and 4 with a greater decrease observed for patients with BW ≥50 kg (LS mean percent change without adjustment: -40.6% with 40 mg Q2W in the lower BW category, and -49.8% with 75 mg Q2W in the higher BW category for Cohort 2 and -31.9% with 150 mg Q4W in the lower BW category, and -59.8% with 300 mg Q4W in the higher BW category for Cohort 4). For Cohort 4, the decrease in calculated LDL-C was maintained at Week 12 (LS mean [SE] without adjustment: -38.6%). The proportion of patients who reached the pre-specified LDL-C targets at Week 8 was compatible with a wider use of

alirocumab in Phase 3 at the doses assessed in Cohorts 2 and 4, but not at the doses evaluated in Cohorts 1 and 3.

The doses in Cohorts 1 and 3, evaluating Q2W (doses of 30 mg for BW <50 kg and 50 mg for BW ≥50 kg) and Q4W (doses of 75 mg for BW <50 kg and 150 mg for BW ≥50 kg) dosing regimen, respectively, did not result in the expected efficacy for this pediatric population and therefore were not retained in the selection of the doses to be evaluated in the Phase 3 study.

Overall, alirocumab was well tolerated at all of the doses assessed in the 4 cohorts. No treatment-emergent serious adverse events (SAEs) were reported in the OLDFI/OLE combined period. Two treatment-emergent adverse events (TEAEs) leading to permanent treatment discontinuation were reported (neutropenia and fatigue). Neither of these TEAEs was considered related to IMP.

In all cohorts, there was no adverse event of special interest (AESI) reported in the OLDFI or OLE period.

Mean concentrations of total alirocumab increased with dose for both Q2W and Q4W dosing regimens. Dose-dependent increase in total PCSK9 and decrease in free PCSK9 and LDL-C were observed. The greatest decrease in free PCSK9 from baseline was observed in Cohort 4, for both BW groups. Low level of immunogenicity was observed. Four patients were noted with positive neutralizing ADA status, of these, 3 had single episodes of neutralizing ADA, and 1 patient in Cohort 1 had 2 episodes of neutralizing ADA post-baseline. No safety concern related to positive anti-drug antibodies (ADA) was raised from the 4 patients with treatment-emergent positive response.

In conclusion, the results showed a positive benefit/risk profile with alirocumab in the pediatric heFH population studied.

The DFI14223 study results were disclosed on *EudraCT* and *clinicaltrials.gov* on 16 August 2019. The synopsis of the approved clinical study report (CSR) is attached herewith.

On behalf of the study team, we thank you for your participation in this very important study.

Kind regards,

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CC: CTOM, GRA, MW, Trial Transparency Managers