Statistical Analysis Plan for Additional Analyses of CYD14 and CYD15 9–16 year-old Study Participants in Preparation for the FDA VRBPAC Meeting March 7, 2019

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1 Introduction

An FDA CBER VRBPAC advisory board meeting is taking place on March 7, 2019, at which Sanofi will ask the advisory panel if they support licensure of the CYD-TDV vaccine in 9-45 year-olds that have evidence of prior exposure/infection with dengue, in the United States and its territories. This SAP describes the statistical analysis plan for addressing objectives that were not studied in previous papers or statistical reports, the results of which may be used as part of the back up slide deck for the VRBPAC meeting. The statistical methods used for these analyses are similar to methods applied previously by the Fred Hutch, where in this report the methods are applied to new study endpoints or to the same endpoints with new follow-up periods.

2 Study Objectives

2.1 Nomenclature for the objectives

The following terms are used, which have been used in previous statistical reports and publications including Moodie et al. (2018), Price, Gilbert and van der Laan (2018), and Sridhar et al. (2018).

- **Hospitalized DENV-Any** is the hospitalization with dengue endpoint of any of the four serotypes [this endpoint was also studied in Sridhar et al. (2018) and in the follow-up report that repeated the TMLE analysis for complete follow-up through Month 72 post-enrollment]

- **Month 13 average $\mathbf{PRNT_{50}}$ titer** is the Month 13 "average titer" or "AUC-MB" marker used in Moodie et al. (2018) that is defined as a participant's average of her/his log10-transformed serotype-specific $PRNT_{50}$ readouts for all available measurements among the 4 possible measurements [before averaging, $PRNT_{50}$ values at the lower limit of assay quantification value of 10 (LLoQ < 10) are set to have value 5] m

- **Month 0 average $\mathbf{PRNT_{50}}$ titer** is the same as Month 13 average $PRNT_{50}$ titer except measured based on a Month 0 (i.e., baseline) sample

- **Month 13 CoVE** is a Month 13 average $PRNT_{50}$ titer correlate of vaccine efficacy against the hospitalized DENV-Any endpoint through to the end of CYD14/15 study follow-up at Month 72 post-enrollment. This parameter is the same as in Moodie et al. (2018) except follow-up

is through Month 72 instead of through Month 25. Vaccine efficacy is measured as one minus the ratio (vaccine/placebo) of the cumulative rate of the endpoint through Month 72.

- **Month 0 CoVE** is a Month 0 average $PRNT_{50}$ titer correlate of vaccine efficacy against the hospitalized DENV-Any endpoint through to the end of CYD14/15 study follow-up at Month 72 post-enrollment. This parameter is the same as in Moodie et al. (2018) except follow-up is through Month 72 instead of through Month 25.

- **Baseline seronegative based on $\mathbf{PRNT_{50}}$**: A participant is baseline seronegative if all available Month 0 $PRNT_{50}$ measurements are below the LLoQ.

- **Baseline seropositive based on $\mathbf{PRNT_{50}}$**: A participant is baseline seropositive if at least one of the available Month 0 $PRNT_{50}$ measurements is above the LLoQ.

- **Baseline seronegative based on Month 13 NS1**: A participant is baseline seronegative if s/he has Month 13 NS1 data and the NS1 titer readout is less than or equal to 9.

- **Baseline seropositive based on Month 13 NS1**: A participant is baseline seropositive if s/he has Month 13 NS1 data and the NS1 titer readout is greater than 9. These baseline seronegative and seropositive definitions were used in supplementary analyses of baseline serostatus in Sridhar et al. (2018).

- **Month 13 visit in CYD14 and CYD15:** The time point corresponding to Visit (V) 06 for CYD14 and CYD15, occurring approximately 1 month after the third study injection and approximately 13 months after the first study injection; because of variation in the actual time of occurrence, this study visit may have occurred earlier or later than 13 months after the first injection

- **Month 72 post-enrollment in CYD14 and CYD15** Month 72 post-enrollment indicates the date occurring exactly 72 months (to the day) after the first study injection.

2.2 Study objectives

The following two study objectives are addressed by this SAP:

1. [**Month 0 coVE Hospitalized DENV-Any**] To assess in CYD14+CYD15 9–16 year-olds pooled the association between Month 0 average $PRNT_{50}$ titer and VE against hospitalization with dengue of any serotype occurring after Month 0 through to the end of the CYD14/15 study follow-up, for all participants

2. [**Month 13 coVE Hospitalized DENV-Any**] To assess in CYD14+CYD15 9–16 year-olds pooled the association between Month 13 average $PRNT_{50}$ titer in vaccine recipients and VE against hospitalization with dengue of any serotype occurring after Month 13 through to the end of the CYD14/15 study follow-up, for all participants and for the baseline seronegative and seropositive subgroups defined based on Month 13 NS1 titer

3 Study Cohorts

3.1 Study cohorts

The analyses of the two objectives are based on data from the two Phase 3 efficacy trials of the CYD-TDV vaccine, CYD14 and CYD15 (Capeding et al., 2014; Hadinegoro et al., 2015; Villar et al., 2015). All analyses of CYD14 and CYD15 for the two objectives focus on the CYD14+CYD15 studies pooled in 9–16 year olds. By "study cohort" we mean the cohort of study participants with data included in the analysis, although for estimating sampling weights data from the larger cohorts are also used. The following list defines the study cohorts that are analyzed to meet each of the study objectives, where next to each cohort definition we note the set of objectives addressed based on the cohort:

- [**Month 0 Hospitalized DENV-Any Case-Cohort**] Membership in this case-cohort is defined by being in either the **Baseline seronegative by $PRNT_{50}$** or **Baseline seropositive by $PRNT_{50}$** subgroups and either (i) being a case, defined as having a hospitalized DENV-Any event after the Month 0 visit, or (ii) being a control, defined as having a study visit at or after Month 13 and never having a registered hospitalized DENV-Any event at any time during follow-up. Note that this case-cohort is all in the immunogenicity subset. **(Objective 1)**

- [**Month 13 Hospitalized DENV-Any Case-Cohort**] Membership in this case-cohort is defined by having Month 13 average $PRNT_{50}$ mea-

sured and either (i) being a case, defined as having a hospitalized DENV-Any event after the Month 13 visit, or (ii) being a control, defined as having a study visit at or after Month 13 and never having a registered hospitalized DENV-Any event. **(Objective 2)**

- [**Month 13 Hospitalized DENV-Any Baseline Serostatus Case-Cohort**] Membership in this case-cohort is defined by being in either the **Baseline seronegative by Month 13 NS1 titer** or **Baseline seropositive by Month 13 NS1 titer** subgroups and either (i) being a case, defined as having a hospitalized DENV-Any event after the Month 13 visit, or (ii) being a control, defined as having a study visit at or after Month 13 and never having a registered hospitalized DENV-Any event. **(Objective 2)**

4 Study Endpoints

For both objectives, the study endpoint of CYD14 and CYD15 is the same as analyzed previously:

1. Hospitalized DENV-Any defined above, occurring after Month 0 or after Month 13 through to end of the CYD14/15 study follow-up (Month 72 post enrollment)

5 Statistical Analysis

All confidence intervals and p-values are 2-sided, and there are no adjustments for multiplicity of hypothesis testing, unless noted. We describe the planned statistical analyses for each objective in turn, re-stating the objectives for convenience.

5.1 Objective 1

[**1. Month 0 coVE Hospitalized DENV-Any**] To assess the association between Month 0 average PRNT_{50} titer and VE against hospitalization with dengue of any serotype occurring after Month 0 through to the end of the CYD14/15 study follow-up, for all participants

The relevant portion of the analysis plan used in Moodie et al. (2018) for studying Month 0 average PRNT_{50} titer as a coVE for VCD DENV-Any

through Month 25 is applied for studying Month 13 average $PRNT_{50}$ titer as a coVE for hospitalized DENV-Any through Month 72. In particular:

1. [**Analyses Including All Participants**] The same logistic regression methods and code used in Moodie et al. (2018) are applied, with the same baseline covariate adjustment for age categories (≤ 11, > 11), sex, and country. No weighting is required because we work exclusively with the immunogenicity subset. All participants in the **Month 0 Hospitalized DENV-Any Case-Cohort** are included in the analysis. The analyses study quantitative Month 0 average $PRNT_{50}$ titer as a coVE. Several regression models of baseline titers will be assessed, and both tabular and graphical output will be produced to show the estimated correlates of risk and correlates of VE models and 95% bootstrap pointwise confidence intervals.

5.2 Objective 2

[**2. Month 13 coVE Hospitalized DENV-Any**] To assess the association between Month 13 average $PRNT_{50}$ titer in vaccine recipients and VE against hospitalization with dengue of any serotype occurring after Month 13 through to the end of the CYD14/15 study follow-up, for all participants and for the baseline seronegative and seropositive by the Month 13 NS1 titer subgroups

1. [**Analyses Including All Participants**] The same primary coVE method applied in Moodie et al. (2018) is applied, with the same baseline covariate adjustment for age, sex, and country. The failure time is defined as the number of days from the Month 13 visit until hospitalized DENV-Any that may occur through Month 72 post-enrollment, and the censoring time also may occur through Month 72 post-enrolment. All participants in the **Month 13 Hospitalized DENV-Any Baseline Serostatus Case-Cohort** are included in the analysis. Similar graphical output as in Moodie et al. (2018) is produced (Figure 5 from Moodie et al. 2018 for this objective).

2. The analyses use inverse probability weights assigned to each participant included in the analysis – which is all **Month 13 Hospitalized DENV-Any Baseline Serostatus Case-Cohort** participants, all of whom have Month 13 average $PRNT_{50}$ titer data measured and baseline serostatus defined by Month 13 NS1 available. These weights are defined

as reciprocals of estimates of the probability a given included participant was sampled into the analysis. For hospitalized DENV-Any cases, this probability is estimated by 1. For hospitalized DENV-Any controls, this probability for the overall analysis is estimated as the empirical fraction of participants observed to attend the Month 13 study visit or a later study visit without ever registering a hospitalized DENV-Any endpoint that also have Month 13 average $PRNT_{50}$ titer data and baseline serostatus defined by Month 13 NS1. This probability is computed separately for each trial (i.e., stratified sampling weights). For the analyses of baseline seronegative and baseline seropositive subgroups, the probability a given included participant was sampled into the analysis has numerator estimated the same as for the overall analysis, restricting to the baseline serostatus group under consideration. The denominator of this probability for the baseline seronegative analysis is estimated as the denominator estimate from the overall analysis multiplied by a fraction f, which is the fraction of the immunogenicity subset with Month NS1 titer measured and ≤ 9. The denominator of this probability for the baseline seropositive analysis is estimated as the denominator estimate from the overall analysis multiplied by the fraction (1-f). Again these numerators and denominators are estimated separately for the two trials.

3. [**Analyses by Baseline Serostatus by Month 13 NS1 Titer**] The same analyses as in 1. are done, except in the two baseline subgroups of the **Month 13 Hospitalized DENV-Any Baseline Serostatus Case-Cohort** defined above. The same weights described above are used.

4. The set of covariates to adjust for may be coarsened if the number of hospitalized DENV-Any endpoints is too-few to stably support all of the covariates age, sex, and country.

5.2.1 Additional details As in Moodie et al. (2018), coVEs are assessed using the VE curve effect modification framework, which studies how VE varies over vaccinated subgroups defined by Month 13 average $PRNT_{50}$ titer. The method of Juraska, Huang, and Gilbert (2018) is used, implemented in the R package `pssmooth` (Juraska, 2018), incorporating hinge models (Fong et al., 2017) of dengue risk conditional on Month 13 average titer and baseline covariates. The method is applied to produce pointwise and simultaneous bootstrap-based Wald 95% CIs for the VE curve and to test whether VE varies across vaccinated subgroups defined by the Month 13 average titer.

The code for producing the results is available upon request.

References

Maria Rosario Capeding, Ngoc Huu Tran, Sri Rezeki S Hadinegoro, Hussain Imam HJ Muhammad Ismail, Tawee Chotpitayasunondh, Mary Noreen Chua, Chan Quang Luong, Kusnandi Rusmil, Dewa Nyoman Wirawan, Revathy Nallusamy, et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. *The Lancet*, 384(9951):1358–1365, 2014.

Y Fong, PB Gilbert, and S Permar. chngpt: Threshold regression model estimation and inference with applications in immunological assay data. *BMC Bioinformatics*, 18(454), 2017.

Sri Rezeki Hadinegoro, Jose Luis Arredondo-García, Maria Rosario Capeding, Carmen Deseda, Tawee Chotpitayasunondh, Reynaldo Dietze, HI Hj Muhammad Ismail, Humberto Reynales, Kriengsak Limkittikul, Doris Maribel Rivera-Medina, et al. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. *New England Journal of Medicine*, 373(13):1195–1206, 2015.

Michal Juraska. *pssmooth: Flexible and Efficient Evaluation of Principal Surrogates/Treatment Effect Modifiers*, 2018. R package version 1.0.1.

Michal Juraska, Ying Huang, and Peter B Gilbert. Inference on treatment effect modification by biomarker response in a three-phase sampling design. *Biostatistics*, 2018.

Z Moodie, M Juraska, Y Huang, Y Zhuang, Y Fong, LN Carpp, SG Self, L Chambonneau, R Small, N Jackson, F Noriega, and PB Gilbert. Neutralizing antibody correlates analysis of tetravalent dengue vaccine efficacy trials in Asia and Latin America. *Journal of Infectious Diseases*, 217(5): 742–753, 2018.

B Price, PB Gilbert, and MJ van der Laan. Estimation of the optimal surrogate based on a randomized trial. *Biometrics*, 2018.

Saranya Sridhar, Alexander Luedtke, Edith Langevin, Ming Zhu, Matthew Bonaparte, Tifany Machabert, Stephen Savarino, Betzana Zambrano, Annick Moureau, Alena Khromava, et al. Effect of dengue serostatus on dengue vaccine safety and efficacy. *New England Journal of Medicine*, 2018.

Luis Villar, Gustavo Horacio Dayan, José Luis Arredondo-García, Doris Maribel Rivera, Rivaldo Cunha, Carmen Deseda, Humberto Reynales, Maria Selma Costa, Javier Osvaldo Morales-Ramírez, Gabriel Carrasquilla, et al. Efficacy of a tetravalent dengue vaccine in children in latin america. *New England Journal of Medicine*, 372:113–123, 2015.