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Dear Charlie and Clare,

Re: Single Technology Appraisal – aflibercept in combination with irinotecan and fluorouracil-based therapy for the treatment of metastatic colorectal cancer which has progressed following prior oxaliplatin-based chemotherapy

The Evidence Review Group (Centre for Reviews and Dissemination, University of York) and the technical team at NICE have now had an opportunity to take a look at submission received on the 15 February by Sanofi. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **17:00, 20 March 2013**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments, or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Ahmed Elsada – Technical Lead (ahmed.elsada@nice.org.uk). Any

procedural questions should be addressed to Jeremy Powell – Project Manager (jeremy.powell@nice.org.uk) in the first instance.

Yours sincerely

Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Further study reports required

A1. **Priority Question:** Further to our e-mail on 22nd February regarding the ERG's request for additional documents, please could you reconsider providing a copy of the clinical study report for the VELOUR trial.

A2. **Priority Question:** Please provide a full report of the meta-analysis of aflibercept adverse events referred to on p.71 of the submission, which included the VELOUR, VITAL and VANILLA trials. Please also provide full adverse event results individually from the VITAL and VANILLA trials.

A3. Please provide the study protocol and results of the survey of UK clinical oncology experts used to estimate community-based care and personal and social care related costs included in the economic model.

A4. As indicated on p. 40 of the submission, please provide any available results for the ongoing non-randomised trial (ASQoP - AFLIBC06097) investigating the safety of aflibercept and the HRQL in patients with mCRC (described in Table A-2 of the submission).

A5. If available, please provide the report for the trial of aflibercept+FOLFOX in the first line treatment of patients with metastatic colorectal cancer (AFFIRM). If not available, please provide any further details of the trial and any available results.

Outcomes in the VELOUR trial: Overall Survival

A6. Since the analysis is mainly based on mean survival times, please provide mean survival for those patients who had died at the time of the most recent

data analysis, by treatment group, including for the subgroups. For each analysis, please state the parametric distribution used to estimate the mean.

A7. Please provide log-cumulative hazard plots for overall survival equivalent to Figure B-6 (P58) with readjusted (widened) scale so as to permit visual inspection of plots beyond Log [time (14 day cycles)] ≥ 1. In addition, please reduce the size of the markers for both treatments, as the circles and squares used are too large.

A8. **Priority Question:** Please complete table B9 (p. 55) by providing overall survival HR for aflibercept plus FOLFIRI versus placebo plus FOLFIRI estimates, as well as corresponding standard deviations, for the following time (t) intervals:

i) 18 < t ≤ 24 months;

ii) 24 < t ≤ 30 months;

iii) 30 < t ≤ 36 months.

Please include the number of patients censored per treatment arm for each interval (including t ≤ 6 months, 6 < t ≤ 12 months, 12 < t ≤ 18 months, 18 < t ≤ 24 months, 24 < t ≤ 30 months, and 30 < t ≤ 36 months), as well as the number of patients at risk at t = 36 months.

A9. **Priority Question:** Please provide a figure with the fitted log-logistic functions extrapolated to 15 years with the Kaplan Meier curves overlaid. Please display both treatment arms in the same figure.

A10. Please add to Figures B-4 (p. 56) and B-5 (p. 57) the overall survival curve resulting from the fitting of the Gompertz distribution for which AIC/BIC results are presented in table B10 (p. 56).

A11. On p. 59 it states that the curves were truncated at 15 years to avoid implausibly long survival times. However, in the ERG's opinion, 15 years is still too long for this population. Therefore, please present the estimates with the analysis truncated at 5 and 10 years, along with both mean and median survival times for each model.

Outcomes in the VELOUR trial: Progression Free Survival

A12. Disease progression was defined as: at least a 20% increase in the sum of the longest diameter of target lesions; unequivocal increase in the size of

non-target lesions; or the appearance of one or more new lesions. Please provide the rationale for this definition. Results were based on independent review committee (IRC) tumour assessment, with investigator assessment of progression used in sensitivity analysis. Please provide separate results for both IRC and investigator assessed PFS.

A13. Please report the mean and median PFS with 95% CI for the following parametric and non-parametric functions, Kaplan Meier, Weibull, log-normal, log-logistic, exponential and Gompertz. Please report values for both treatment arms.

A14. Please report the mean and median PFS with 95% CI for the functions mentioned above, but assuming the proportional hazards assumption. Please report values for both treatment arms.

A15. Please present equivalent results for the Gompertz distribution in table B20 (p. 85).

Outcomes in the VELOUR trial: Response rate

A16. Table B5 states the primary and secondary outcomes and how they were measured, but not the timings. The journal article by Van Cutsem et al. (2012) states that disease assessment was performed every 6 weeks until documented progression. Please confirm that this disease assessment was for response rate, as well as disease progression.

Outcomes in the VELOUR trial: Time to Treatment Discontinuation

A17. Please provide legible figures for B-13 and B-14 by using different colours for the curves.

A18. Please provide the mean and median times to FOLFIRI discontinuation in each arm and the mean and median time to aflibercept discontinuation, for any reason for discontinuation, and for each reason for discontinuation separately (i.e. adverse event, disease progression, patient request, etc).

A19. **Priority Question:** Please provide more detail on further lines of treatments, namely:

a) Proportion of patients in each treatment arm:

i) On any active treatment and on each specific active treatment after discontinuation;

ii) Who underwent liver metastases resection (for ITT and liver metastases only subgroup).

b) Mean number of cycles of any subsequent active treatment by treatment arm:

i) After early discontinuation of the second line treatment;

ii) After progression.

A20. **Priority Question:** Please clarify the difference between “Time to second-line treatment discontinuation” and “Time to second-line early discontinuation”. In addition, please explain how does “Time second-line treatment discontinuation” curve differs from the PFS curve.

A21. For both “Time to second-line treatment discontinuation” and “Time to second-line early discontinuation”, please present the following descriptive statistics for non-parametric curves: mean, median, standard deviation and number of observations by treatment arm.

A22. It is stated in p. 88 of the submission that further details for the time to second-line treatment discontinuation were provided in appendix 14, but this appendix refers only to PFS and OS data. Please provide these missing details in appendix 14.

A23. Please clarify which survival curves (parametric or non-parametric) were used for “time to second-line treatment discontinuation” and “time to early second-line treatment discontinuation” for the cost-effectiveness analysis results (reproduced in tables 10-24 and 10-24 in appendix 16) of the i) liver metastases only subgroup, and ii) ITT excluding patients relapsing within 6 months of adjuvant therapy subgroup. Please, could you also justify the rationale for selecting the survival curves for each subgroup.

A24. Please provide tables equivalent to tables B21 and B22 (p. 88), as well as figures equivalent to figures B-13 and B-14 (p. 89) for the i) liver metastases only, and ii) ITT excluding patients relapsing within 6 months of adjuvant therapy. Please ensure that figures are legible and that different colours are used for each curve.

Patient Sub-groups

A25. Please provide duration of second-line treatment, number of administrations per cycle, dose intensity per administration, weight and BSA distributions, and AE probabilities for the i) liver metastases only subgroup, and ii) ITT excluding patients relapsing within 6 months of adjuvant therapy subgroup. These data could not be found in Appendix 15.

Section B: Clarification on cost-effectiveness data

Utility Study

B1. Please provide the mean and median time since progression for those patients in the utility study that had progressed.

B2. Please provide the mean and median time since diagnosis for those patients in the utility study that had progressed, as well as for those that were in stable states.

Adverse events

B3. On p. 89 it is mentioned that six additional rare events were included in the evaluation, as they were considered relevant by the clinical advisory board. Please name those events, and provide further explanation on the rationale underlying the clinical advisory board recommendation to include them.

Costs

B4. Please clarify what is included in ‘regimen changes’ costs for Stable, discontinued second-line therapy, and Progressed health states respectively, presented in table B24 (p. 93-94).

Model

B5. **Priority Question:** Please provide a version of the economic model that incorporates the use of the Gompertz distribution to model PFS and OS for the ITT population and subgroups. The model should include data that allows the modelling of the curves separately or as a proportional hazards model. If this is not possible please provide the full set of distribution parameters, variance and covariance matrices, and Cholesky decomposition matrices for the Gompertz distribution.

B6. **Priority Question:** In the Efficacy Inputs sheet cell F7 there is a comment stating that the Kaplan Meier option is not available in the current version of the model. Nonetheless, there is a Kaplan Meier option on the drop-down list. Please clarify what does this option refer to, and if it is not to the Kaplan Meier curve for OS, please include a version of the model that incorporates the OS Kaplan Meyer curve from VELOUR study to model OS for ITT and subgroups.

B7. There are two possible Kaplan Meier curves estimates for the "Early 2nd line treatment discontinuation while in stable health state" curve in the Efficacy Inputs sheet: i) IRC,and ii) Investigator. However, in the submission there is no mention that this parameter could take different values depending on IRC or investigator assessment (as was the case for PFS). Please clarify the rationale for the inclusion of these curves and the differences between them.

Results

B8. Please provide equivalent results to those presented in table 10-24 (p. 60 in Appendices) for the patient subgroups that had no liver metastases and those that had metastases in the liver and other locations.

B9. Please provide equivalent results to those presented in table 10-25 (p. 62 in Appendices) for the patient subgroup that corresponds to patients who had relapsed on or within 6 months of adjuvant treatment in the VELOUR trial, and who were excluded from the ITT population in the post-hoc subgroup analysis.

B10. Please report the ICER using the OS HR from the covariate models and the ICERs for the 5% and 95% CI bounds of these HRs.

Sensitivity analyses

B11. Please report base case values and upper and lower bounds for all parameters explored in the one way sensitivity analyses for ITT and both subgroups analyses.

Section C: Textual clarifications and additional points

C1. In Section 4, the submission states that aflibercept is the only drug to demonstrate a statistically significant OS benefit in combination with FOLFIRI in such patients (patients with mCRC who have been treated with an

oxaliplatin-based therapy). Please provide the supporting references for this statement.

C2. Please clarify the a priori subgroup relating to liver metastases. On p. 49 (Baseline characteristics) it suggests the subgroups are whether patients had liver metastases or not.

C3. Please explain why the drug name aflibercept (and related terms) was not searched for in the search strategy.

C4. Please state which host was used for the EMBASE search strategy, and explain why MESH terms were used, rather than EMTREE terms in the EMBASE search at line 1.

C5. There is some text missing on the row referring to the Wiering (2011) study on table B26 (p. 107). Please complete the table.

C6. Please complete table B4 (p. 44-45) for demographic characteristics by including geographical region (Western Europe, Eastern Europe, North America, South America or other), and mean age, for each treatment group.

C7. Please clarify why the mean treatment duration with Aflibercept+FOLFIRI in the VELOUR study is reported as 10.4 cycles in table A-3 (p. 23) and 12.1 cycles in table B35 (p. 131).