NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Nintedanib for treating idiopathic pulmonary fibrosis [ID752]

Dear [redacted]

The Evidence Review Group, Southampton Health Technology Assessments Centre, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 1 May 2015 by Boehringer Ingelheim. 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 **6pm** on 10 June 2015. 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 Sophie Laurenson, Technical Lead (sophie.laurenson@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

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Section A: Clarification on effectiveness data

Clinical trials

A1. **Priority question:** Please confirm the number of UK participants in each of the nintedanib trials (TOMORROW and INPULSIS) and provide their baseline characteristics (please replicate Tables 16 and 17 of the company submission for UK sites only).

A2. **Priority question:** Figures 9 and 10 of the company submission include reasons for treatment discontinuation and non-completion in the INPULSIS trials. Please provide an updated Figure 8, to include the reasons for non-completion in the TOMORROW trial (this should also include patient numbers).

A3. **Priority question:** On page 65 of the company submission it is stated that subgroup analyses of patients with a baseline forced vital capacity (FVC) of ≤70% compared with >70% of the predicted value were conducted using data from the INPULSIS trials. Please provide a rationale for why these FVC values were chosen.

A4. **Priority question:** Please provide the correct reference for the statement on page 66 of the company submission: "the results of the subgroup analysis for nintedanib did not find any statistically significant differences in outcomes by subgroup". The reference cited in the company submission (Costabel, 2014) is about pirfenidone.

Systematic literature review and network meta-analysis

A5. **Priority question:** Please supply the WinBUGS code for the network meta-analysis (section 4.10 of the company submission).

A6. **Priority question:** Tables 29–37 of the company submission present results of the network meta-analysis. These tables indicate that the denominator (for proportions of patients) for each outcome is 'patients at risk' (and for the INPULSIS trials it can be seen that there are fewer 'patients at risk' than 'patients randomised'). Please describe how 'patients at risk' was defined. Is the same definition used in the trials of comparator drugs which are presented in these tables?

A7. Please clarify the processes used for data extraction of the studies included in the systematic literature review. On page 37 of the company submission it is stated that "Data extraction was performed by one researcher, documented in Microsoft Excel data extraction forms and reviewed by a second researcher." Please clarify whether or not this means that the second reviewer checked the

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data extracted by the first for accuracy. Additionally, please clarify how discrepancies in the reviewers' judgements were resolved.

A8. In Figure 5 of the company submission it is stated that 6 references were identified from regulatory agencies (top right-hand side of the PRISMA diagram). Please clarify whether these are the 6 excluded studies listed in Table 9 of the company submission.

A9. Please clarify if the search strategy used for the network meta-analysis was the same as the one used for the systematic review (section 4.10 of the company submission). If not, please specify any differences.

Data clarifications and reference requests

A10. **Priority question:** Please provide a citation, and the reference document(s) for the acute exacerbations data presented in Table 30 of the company submission, for the TOMORROW trial. These data are not available in the publication provided (Richeldi 2011).

A11. **Priority question:** Table 31 of the company submission presents the results from the network meta-analysis for loss of lung function, defined as a decline of 10% or more in forced vital capacity percent predicted (FVC%Pred; a standardisation of forced vital capacity). On page 93 of the company submission it is stated that the FVC%Pred data for the nintedanib trials (TOMORROW and INPULSIS) were obtained from a post-hoc analysis, based on observed data only.

i. Table 31 presents 2 sets of data for each trial (one set excluding deaths, one set including deaths). Please provide a justification for presenting 2 data sets.

ii. Please provide a citation, and the reference document(s), for the post-hoc analysis of the TOMORROW and INPULSIS trials.

iii. What was the quantity of missing data in each arm of each trial in the post-hoc analysis of the TOMORROW and INPULSIS trials? For each trial arm, please provide the number of participants not contributing data and the total number of participants (n/N).

A12. **Priority question:** On page 95 of the company submission it is stated that the progression free survival data for the nintedanib trial presented in Table 32 (Richeldi 2014) were obtained from a post-hoc analysis. Please provide a citation, and the reference document, for this post-hoc analysis.

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A13. **Priority question:** The data for the INPULSIS trials (Richeldi 2014) presented in Table 37 of the company submission do not correlate with the data in Figure 9 of the company submission. Have data for INPULSIS II been omitted from Table 37 in error? Alternatively, was a different source used for the INPULSIS data in Table 37? If so, please provide the reference.

A14. **Priority question:** Table 122 of the company submission presents odds ratios for overall discontinuation from the all evidence scenario of the network meta-analysis (fixed effects model). These data are used in the cost-effectiveness model. The data in Table 122 do not match the data in Table 90, suggesting that there is an error in one of these tables. Please check the data in these tables and provide corrected tables. Please also provide a corrected model if appropriate.

A15. On page 28 of the company submission, it is stated that each year 5000 patients with IPF die. Please provide the correct reference for this statement. The reference provided is a conference abstract report of the INPULSIS trial and does not provide this mortality information.

A16. The company submission does not present the results of the sensitivity analyses to investigate missing data effects, using multiple imputation approaches. For the INPULSIS trials this is available in the supplementary appendix to the published paper. Please provide the equivalent results for the TOMORROW trial.

A17. Please explain the following discrepancies in the reporting of adverse events leading to discontinuations:

i. Figure 9 (24 people in the placebo group of INPULSIS-1 prematurely discontinued due to adverse events) compared with Table 93 (22 people in the placebo group of INPULSIS-1 had adverse events leading to discontinuation)

ii. Figure 10 (37 people receiving nintedanib in the of INPULSIS-2 trial prematurely discontinued due to adverse events) compared with Table 93 (58 people in the nintedanib arm of INPULSIS-2 had adverse events leading to discontinuation)

iii. Figure 10 (25 people receiving placebo in the INPULSIS-2 trial prematurely discontinued due to adverse events) compared with Table 93 (33 people in the placebo group of INPULSIS-2 had adverse events leading to discontinuation).

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A18. Please provide a citation and the reference document(s) used for the TOMORROW trial data in Table 33 of the company submission (6 Minute Walk Test). These data are not presented in Table 18 of the submission and are not available in the TOMORROW publication (Richeldi 2011).

A19. Table 34 of the company submission presents the results from the network meta-analysis for serious cardiac events.

i. What is the definition of serious cardiac events?

ii. Please provide a citation and the reference document(s) used for the TOMORROW trial data in Table 34. These data are not presented in Table 18 and not available in the TOMORROW publication (Richeldi 2011).

iii. Please clarify the source used for the INPULSIS trial data in Table 34. Is it Table S10 of the appendix to the published paper ('serious adverse event cardiac disorder')?

A20. Table 35 of the company submission presents the results from the network meta-analysis for serious gastrointestinal (GI) events:

i. What is the definition of serious GI events?

ii. Please clarify the source used for the TOMORROW trial data in Table 35. Is it Table S7 of the appendix to the published paper ('severe diarrhoea')? If so, please provide a justification for why the 'serious diarrhoea' data in Table S7 were not used.

iii. Please provide a citation and the reference document(s) used for the INPULSIS trial data in Table 35.

Section B: Clarification on cost-effectiveness data

Utility values

B1. **Priority question:** Please provide more details on collection of utility values in the INPULSIS clinical trials, including:

i. how the data were collected

ii. how frequently the data were collected

iii. how many patients contributed data

iv. the quantity of missing data.

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B2. Please provide the correct reference for the disutility values reported in section 5.4.6 of the company submission. These data are not available in the reference cited (Ara and Brazier 2010).

Other model inputs

B3. **Priority question:** Please provide more details on collection of resource values in the INPULSIS clinical trials used in the model including:

i. how the data were collected

ii. how frequently the data were collected

iii. how many patients contributed data

iv. the quantity of missing data.

B4. **Priority question:** In the model, only severe adverse events that occurred in the best supportive care arm were included (as described on pages 180–1 of the company submission). Please provide details of any severe adverse events that occurred during treatment with nintedanib or pirfenidone that did not occur in the best supportive care arms of the clinical trials included in the network meta-analysis. Please describe the potential cost and clinical effectiveness impacts of these severe adverse events.

B5. **Priority question:** Please provide a justification for using the outpatient procedure (OPROC) code instead of inpatient costs (NEL, NES) for the cost of mechanical ventilation during an inpatient stay (Table 141 and 159 of the company submission).

B6. On pages 65 and 182 of the company submission it is stated that liver enzyme elevations were assumed to be asymptomatic for patients (and therefore there was no disutility or additional costs associated with them in the model). Please provide a justification for this assumption.

Validation of models

B7. **Priority question:** The post-hoc analysis (reference 97 of the company submission) was the most frequently cited reference for the model, but the reference has not been provided. Due to this, the validity of the analyses conducted based on these data could not be fully checked. Please provide reference 97: Ingelheim B. data on file - phase III trial (trial no. 1199.32 and 1199.34) post-hoc analysis. 2014.

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B8. **Priority question:** Please explain how the exponential models were fitted in Figure 44 of the company submission (including the time-horizons that were considered). It appears that the model does not fit the data very well (it appears to be fixed to the first and last point, but not fixed to any in-between). Please provide an explanation for this.

B9. **Priority question:** In Table 169 and Figure 66 of the company submission, model projections are compared with clinical trial data for best supportive care. These comparisons are made for nintedanib in Table 170 and Figure 67. However, this has not been done for any pirfenidone trial. Please compare the model projections for pirfenidone to pooled pirfenidone data from the CAPACITY and SP2&3 trials (replicating Tables 169–70 and Figures 66–7).

B10. **Priority question:** Figure 65 of the company submission shows that the fit of proportional hazards model for overall survival is not as good for pirfenidone as for nintedanib (Figure 64) or best supportive care (Figure 63). The model will underestimate overall survival in the first year of treatment with pirfenidone, and this underestimation will increase in magnitude over time. As survival is one of the primary drivers of the model, please conduct an analysis where proportional hazards are not assumed for overall survival with pirfenidone. Please provide tabulated survival data for this analysis. Please also provide tabulated survival data for pirfenidone from the loglogistic, Weibull, and Gompertz models which were presented in Figure 65 of the submission.

B11. Please describe how the proportional hazards assumptions were checked for validity in each of the various survival models used for the economic model.

Clarifications and additional analyses

B12. The loglogistic curve for nintedanib is missing from Figure 42 of the company submission (although it is listed in the figure legend). Please provide an updated Figure 42.

B13. Figures 41 and 42 of the company submission present overall survival extrapolations for placebo, nintedanib and pirfenidone. The figures compare these models with data from the study by Kondoh et al. (where data from Kondoh et al. is broken into 2 patient cohorts: ‘with exacerbations’ and ‘without exacerbations’).

i. Please provide tables and graphs of the overall survival data with best supportive care from the INPULSIS trials, broken down by exacerbation status (‘with exacerbations’ and ‘without exacerbations’). Please compare these (in the same tables and graphs) with the Kondoh et al. survival data presented in Figure 41 and Figure 42 of the submission.

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ii. Please provide a sensitivity analysis using pooled survival data from Kondoh (that is, combining the 'with' and 'without exacerbations' cohorts) as an alternative to overall survival data from the INPULSIS trials (if this is possible based on the data available in the Kondoh publication). Please present full cost-effectiveness results for this alternative analysis.

B14. Please update hospitalisation costs (£303.73; Tables 141, 158 and 159 of the company submission) to 2012-13 NHS Reference costs and provide details of what data were used to calculate the average cost per day on treatment. Please provide updated model results based on the revised hospitalisation costs.

B15. In scenario 46 of the company's exploratory analyses, a 'stopping rule' is applied to people receiving pirfenidone (page 288 and 291 of the company submission). This explored the effect of patients discontinuing and losing treatment effect when they observe a decline of forced vital capacity percent predicted (FVC%Pred) of 10% or more. Please provide the results of an additional scenario analysis in which the 'stopping rule' is also applied to the nintedanib arm.

Section C: Textual clarifications and additional points

C1. On page 20 of the company submission (under the heading "2. Base-case deterministic analysis for nintedanib vs. BSC"), it is stated that the incremental cost of nintedanib (using the PAS price) compared with best supportive care is a negative number. Please confirm that this should be a positive number.

C2. In Table 18 of the company submission the units for 'Annual Rate of Decline in FVC' are reported in the first column as 'ml/year'. Please confirm whether the units are L/year?

C3. In Table 24 of the company submission, under the column headed 'SpO2,% (SD)', please confirm if the data from Noble et al. 2011 (CAPACITY) trials are 'Use of supplemental oxygen' not Sp02.

C4. In Table 25 of the company submission, under the column headed 'change from FVC from baseline, L – mean (SD)', please confirm if the data from Noble et al. 2011 (CAPACITY) trials are not mean values, rather they are the number of patients with the categorical change in FVC ≥10%.

C5. Table 118 of the company submission presents the incidence and risk of gastrointestinal perforation events. Please confirm if the column headings are the wrong way around (for nintedanib and placebo).

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C6. On page 294 of the company submission, it is stated in the text that Table 189 uses the patient access scheme (PAS) price for nintedanib. The title for Table 189 states that the list price for nintedanib was used:

i. Please clarify which price was used.

ii. Please replicate Table 189 using the PAS price for nintedanib, if appropriate.

iii. Please add the total and incremental costs (including the cost breakdown) to Table 189 (replicating Tables 161–164 from the base case analysis).