NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Single Technology Appraisal (STA)

Imatinib for the adjuvant treatment of gastrointestinal stromal tumours (review of TA196) [ID696]

Dear [redacted],

The Evidence Review Group, Southampton Health Technology Assessment Centre, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 4 February 2014 by Novartis Pharmaceuticals. 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 **5pm on 13th March 2014**. 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 Linda Landells, Technical Lead (Linda.Landells@nice.org.uk). Any procedural questions should be addressed to Nicole Fisher, Project Manager (Nicole.Fisher@nice.org.uk) in the first instance.

Yours sincerely

Frances Sutcliffe
Associate Director – Appraisals

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Centre for Health Technology Evaluation

Section A: Clarification on effectiveness data

A1. **Priority question**: Page 62 refers to a HR (0.43 [95% CI 0.30 to 0.62]) for the high risk group. Please specify what the time period is; is it four years?

A2. **Priority question:** Please clarify which population the overall survival data on page 70 if for (median follow up of 60.2 months for the ACOSOG Z9001 trial). Is it the ITT population or Miettinen high risk population? Please also clarify *"overall population"* in the same paragraph; is it the primary analysis population?

A3. Figure B-2 shows there were 2 rounds of title/abstract screening. Please clarify why there were 2 rounds.

A4. Please provide a reference list for the 6 full papers that were excluded (Figure B-2)

A5. The data for EORTC 62024 trial is only currently available as a conference abstract, which doesn't detail the baseline characteristics. Please clarify the source for the information in Table B-7.

A6. Please confirm whether EORTC 62024 received funding from Novartis

A7. Please specify whether there are any data in the submission to inform sub-group analysis by tumour genetic mutation site (other than the data reported in the SSG XVIII journal publication – Joensuu et al 2012, JAMA, 307, 12, Figure 3).

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** The costs for patients undergoing further surgery following first recurrence are included in the model, however the outcomes for these patients are not. Please can you provide a rationale for including these costs without the outcomes (MS section 7.5.6)

B2. **Priority question:** Please confirm whether the group of patients undergoing further surgery following first recurrence are included in the *"Post recurrence and on imatinib 400mg"* health state (also labelled C). And whether they incur the costs of receiving imatinib (plus costs of monitoring patients on imatinib) and surgery, and experience outcomes (in terms of adverse events, probability of recurrence and quality of life) estimated for imatinib-treated patients. Please provide a rationale for adopting this approach.

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B4. **Priority question:** Please confirm how primary and secondary imatinib resistance is defined in the submission. Please clarify how the economic model takes imatinib resistance into account.

B5. **Priority question:** The ERG have been unable to replicate the adjusted indirect comparison presented on page 151 to 152 of the MS, to determine the off-treatment hazard ratio for recurrence. Full results including estimated standard errors (calculated by ERG) are in **Table 1**, but contrast with the value of 0.344 (0.160 to 0.741) presented in the MS (page 152). The details of the calculations are below. Please could you identify the cause of this discrepancy?

- Page 151 of the MS states that treatment effect of 3 years of adjuvant imatinib vs surgery alone (HR3) can be derived as:
  - log(HR3)=log(HR1)-log(HR2)
    - where HR1 = 1 year of adjuvant imatinib vs surgery alone
    - HR2 = 1 year of adjuvant imatinib vs 3 years of adjuvant imatinib
    - log() indicates the natural logarithm
- The final paragraph provides values, with 95% CIs, for the two hazard ratios on the right hand side of the above equation:
  - HR1 = 0.519 (0.297 to 0.906)
  - HR2 = 0.663 (0.392 to 1.123)
- Putting these values into the above equation gives:
  - log(HR3)=log(0.519)-log(0.663)= -0.656 – (-0.411)= -0.245
    - if log(HR3)= -0.245 then HR3=exp(-0.245)=0.783

Table 1 Hazard ratio for recurrence (estimated by the ERG)

	HR	**selogHR**	**95% CI**
HR1	0.519	0.28480	(0.297 to 0.907)
HR2	0.663	0.26850	(0.392 to 1.123)
HR3	0.783	0.39141	(0.363 to 1.686)

B6. On page 130, the final two sentences of the top paragraph appear to be duplicated. Please confirm whether these are duplications or whether they refer to different groups of patients eligible for sunitinib treatment following recurrence

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- the sentences start with *"The majority of patients (90%) who experience a first recurrence …"*

B7. Please clarify the number of patients whose data was analysed to estimate the baseline risk of recurrence in the comparator arm of the model.

B8. There are discrepancies in the number of patients classified as having high risk disease.

- On page 140 the MS states *"165 patients were classified as having Miettinen high-risk disease…"*
    - This agrees with Table B-13 (page 67 of MS) which indicates that, for the primary analysis, 84 imatinib-treated and 81 placebo patients were classified as Miettinen high-risk (total 165).
- Page 140 also states that *"… retrospective data were available for a further 71 patients … (of which 36 were classified as high risk), leading to … 98 patients in the placebo group."* (an additional 17 patients)
    - This figure agrees with Table B-14 (page 69 of MS) which indicates that, at five year follow-up, 103 imatinib-treated and 98 placebo patients were classified as Miettinen high-risk.

Can you confirm whether the additional 17 placebo group patients identified in the five year analysis as Miettinen high-risk were misclassified (i.e. as not being at high risk) in the primary analysis? Please also indicate the nature of the "retrospective data" that became available at five year follow-up that were not previously available for the primary analysis?

B9. Please clarify the source of the HR for RFS 'on treatment', presented on page 143 of the MS.

- The MS states (page 147) that this is estimated from the 1-year imatinib and placebo arms of the ACOSOG Z90001 trial, calculated using Cox proportional hazards model truncating the data at 12 months, reporting a value of 0.111 (95% CI 0.043 to 0.281) - see pages 143 and 148 of the MS.
- However, the HR reported for Meittinen high risk patients in the primary analysis is 0.265 (0.148 to 0.477) see Table B-13 (page 67 of the MS).

Is the difference between these two results primarily related to truncating at 12 months or due to the retrospective re-classification of patients at high risk?

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B10. There are inconsistencies in the assumptions regarding the treatment effects and the incidence of adverse events, in relation to duration of imatinib treatment.

- Page 143 of the MS states *"treatment effect during the 'on treatment' period was assumed to the same irrespective of the planned treatment duration".*
- In contrast, different monthly probabilities of discontinuation are applied for patients receiving 1-year adjuvant imatinib and those having 3-year adjuvant imatinib.
- The application of different monthly probabilities of discontinuation depending on duration of planned treatment also seems to contradict the statement made in the MS (page 177) that *"[N]o notable increase in adverse events during 3 years of treatment was observed in the SSGXVII/AIO trial when compared with 1 year of treatment … suggesting that longer treatment durations are not associated with a greater incidence or severity of adverse events".*

Please provide a rationale for applying different assumptions to efficacy and adverse events.

B11. Adverse event probabilities for both 1-year adjuvant imatinib and 3-year adjuvant imatinib are based on the SSGXVIII/AIO study. However Table B-18 (page 102 of MS) indicates there are also adverse event data available for the ACOSOG Z9001 study (although this table presents data for the whole population and not Miettinen high-risk sub-group). Please provide a rationale for why only the SSGXVIII/AIO study was used.

B.12 Please confirm whether the hazard ratios derived for on-treatment and off-treatment effects of adjuvant imatinib were estimated using Cox proportional hazards models (page 147 of MS). And whether the hazard ratios derived using the Cox models (and further included in adjusted indirect comparisons) were applied to a variety of baseline survival functions (for surgery alone) derived using fully parametric models.

- If so, please could you provide a rationale for using hazards ratios derived using the Cox models rather than estimates derived using the relevant parametric models?

B.13 Page 155 of the MS states that the monthly probability of discontinuing adjuvant imatinib *"was assumed to be different in the first 6 months of adjuvant treatment and next 6 months".* Please could you provide a rationale for choosing those particular time points?

B.14 Page 155 of the MS presents the proportion of patients discontinuing adjuvant imatinib treatment, but does not indicate the reason for discontinuation. On a previous page (page 153, Table B-29) the monthly probabilities derived from these

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discontinuation values are stated as being 'discontinuation due to adverse events'. Please clarify whether these are all discontinuations or only discontinuations due to adverse events.

B.15 Please clarify what is meant by *"Recurrence was used as a surrogate outcome for death"* (see first paragraph under section 7.3.4; top of page 157)

B.16 Treatment effectiveness is assumed to continue in the off treatment period, please provide a justification for this assumption.

- Please provide scenario analyses that assumes treatment effect declines over time for the off treatment period.

B.18 The model assumes a long-term survival benefit for imatinib, and that the post-recurrence GIST mortality is equal across all treatment arms. Please provide justification for these assumptions.

- Please provide scenario analyses in which the post-recurrence GIST mortality is different between treatment arms, such that the mortality probability is higher on the adjuvant imatinib arms than the control arm.

Section C: Clarification on Process and Confidentiality

C1. **Priority question:** It has been noted that your submission refers to an analysis of crossover data which is currently on-going. It is indicated that results and analyses will be updated and these data incorporated. In line with NICE process, to submit further evidence you will need to make a request to do so, and this is subject to agreement from NICE. To clarify, there may be an opportunity to submit further information at the ACD consultation comments stage: the NICE guide to the STA process published October 2009, states in section 3.5.34: ' *At the ACD consultation stage the Centre Director must agree to accept any new evidence before it is submitted. New evidence will only be accepted if it is likely to affect the provisional recommendations in the ACD. ….*'. Please clarify the timings that both the data and analyses will be available. If this data or analysis is available now, please provide it.

C2. **Priority question:** Much of the data that will be critical to the decision-making is currently marked as academic in confidence. The NICE STA process guide states that confidential information should be kept to an absolute minimum to ensure transparency in the appraisal process. As per compliance with CONSORT, that is, that as a minimum a structured abstract should be made available for public disclosure (please refer here http://www.consort-statement.org/?o=1011 for further

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information), further details need to be made publically available. Examples of such data include the arms of the study and number of people on each arm (currently marked as confidential on page 57 of the submission); particularly given these data are currently available in the public domain. Please reconsider the marking in your submission to ensure that:

- no data that are available in the public domain are marked as confidential
- a structured abstract (for all trials presented) is available for public disclosure

C3. **Priority question:** The confidential marking in the submission is currently inconsistent, the same information is marked as confidential in one area but not in another. NICE takes the protection of your confidential information seriously and discrepancies can present a risk of accidental disclosure. Please be consistent and clear in your marking, and limit marking only to items that are confidential (for example, items such as figure titles should not be confidential). Please readdress the marking to ensure that:

- the marking is consistent
- the marking is appropriate