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28 Feb 2007

Dear Alana,

Health Technology Appraisal: Corticosteroids for the treatment of chronic asthma in adults and children aged 12 years and over – Technology Assessment Report (TAR)

Many thanks for the opportunity for stakeholders to provide comments on the above technology assessment report. AstraZeneca is impressed with the volume of work undertaken by the two assessment groups and is generally supportive of the TAR. In addition, we would like to add a few main comments:

1. **Adjustable dosing with combinations'**

   We believe that as well as comparing fixed dosing regimens of combination inhalers, the TAR should include a discussion on the use of adjustable dosing which allows treatment to be tailored to individual patient's needs. For example, the combination inhaler Symbicort can be administered as Symbicort AMD that maintains asthma control, while reducing exacerbations and drug load compared with fixed dosing.

   Furthermore, we believe that a discussion of the treatment Symbicort SMART® should be included in the TAR. Symbicort SMART is a tailored flexible dosing regime that can potentially increase concordance because patients no longer need to use a separate short-acting beta-agonist (SABA) reliever inhaler. Patients using the Symbicort SMART regime experience fewer daily symptoms, less nighttime waking, a lower corticosteroid load and have fewer severe exacerbations compared with a standard adult dose of fixed dose inhaled corticosteroid/LABA plus SABA as needed.

2. **PenTAG model presented in Appendix 10**

   We would also like to highlight that the modelling approach and base case results in the PenTAG model presented in Appendix 10 appear similar to the AstraZeneca approach, although no discussion of this is provided in

the TAR. AstraZeneca suggests that the similarity between the two approaches and this external validity of the results of the AstraZeneca model is included in the TAR.

3. Single Inhaler Therapy

Finally, we note that within the TAR the term 'single inhaler therapy' is used to refer to combination inhaler therapy. We suggest that this term could lead to confusion by the end user; it is plausible that it may be interpreted as monotherapy. Therefore, for improved clarity we suggest using the term combination inhaler rather than 'single inhaler' throughout the document.

In addition to these main comments please find overleaf further detailed comments from AstraZeneca.

If you have any queries regarding this document or its contents, please feel free to call me on direct telephone number: 01582 836370.

Yours sincerely

David Tyas

Market Access Executive
AstraZeneca UK Ltd

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Executive summary	
XXI	This page contains the conclusion that the more expensive ICS products used at higher dose are more expensive than combination inhaler products, whilst the use of cheaper ICS preparations compared to combination therapy will be cost saving. AstraZeneca would like to point out that the final decision by the healthcare professional considers both the cost and clinical benefit. AstraZeneca suggests the paragraph should close with a sentence that incorporates both cost and clinical benefit, e.g. "The more expensive ICS products used at higher dose are more expensive than combination inhaler products, whilst the use of cheaper ICS preparations compared to combination therapy will be cost saving. <u>However, the choice of individual treatment should take into account both the acquisition cost and the likely clinical benefit to the patient.</u>"
XXII	On this page there is the conclusion that there is no combination inhaler that is cheapest in all circumstances. AstraZeneca agrees that there is unlikely to be an inhaler that is always cheapest. However, AstraZeneca would also like to add that there are a large number of comparators to consider. The assessment group has understandably focused on a subgroup of potential comparators (i.e. fixed dose per day). As well as cost being dependent on the dose required and the preparation used, the way in which the preparation is used also needs to be taken account of. Adjustable dosing of combination inhalers to tailor the therapy to the patients' needs is possible with Symbicort. Within the TAR, studies examining adjustable dosing have been included (Aalbers 2004, Pohl 2005, and FitzGerald 2005) and are discussed in the clinical effectiveness sections. AstraZeneca suggests the sentences, "There are no consistent cost differences between the two inhalers, as the costs depend on the dose required and the preparation used. Therefore there is no combination inhaler which is cheapest in all circumstances." are changed to reflect this, for example: "There are no consistent cost differences between the two inhalers, as the costs depend on the dose required and the preparation used. In addition, <u>the use of adjustable dosing can decrease the cost compared to</u> the equivalent fixed dose. Therefore there is no combination inhaler which is cheapest in all circumstances."
Background	
Page 4	On page 4 it is recognised that severe exacerbations can be life threatening. It is then discussed that most

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	exacerbations can be treated with high doses of inhaled SABAs, although sometimes a short course of oral corticosteroids is also needed. While this is true, from a patient's perspective exacerbations are often frightening episodes that can cause significant morbidity. AstraZeneca suggests that the importance of exacerbations to patients is recognised in the TAR. In addition, definitions of the spectrum of exacerbations ranging from the milder (majority) to the life threatening (less frequent but higher impact on patients) should be included. .
Page 18	In table 2 the TAR describes the pharmacodynamic and pharmacokinetic characteristics of the currently available ICS. This is broken down by ICS and device. Budesonide is available in different devices and AstraZeneca suggests that the figures for budesonide via Turbohaler (DPI) are added. This would make it consistent with the details given for the other ICS in the table. AstraZeneca suggests the following details are added in the "Pulmonary bioavailability (device) [%]" column for BUD: "38% (DPI-TBH)". *TBH – Turbohaler. The reference for the bioavailability is taken from: Thorsson L, Edsbäcker S, Conradson TB. Lung deposition of budesonide from Turbuhaler is twice that from a pressurized metered dose inhaler P-MDI. European Respiratory Journal 1994;7:1839-44.*
Page 23	On this page it describes two combination ICS and a LABA products available. AstraZeneca suggest that there should also be a discussion of the different dosing regiments as well as the discussion of the combination product itself. For example, Symbicort SMART is a tailored regime where patients no longer need to use a separate short-acting beta-agonist (SABA) reliever inhaler.) To reflect this AstraZeneca suggest the text should be amended with: **"Combination products available** There are currently two combination products containing an ICS and a LABA licensed for use in adults in England and Wales. BUD combined with FF (BUD/FF) is available in DPIs (Symbicort® Turbohaler [Astrazeneca]). Symbicort can be taken as a fixed dose, adjustable maintenance dosing (AMD), and as Symbicort SMART®…" In addition, on page 438 it states "The use of single inhaler therapy not only provides a simpler treatment regimen, but may also enhance concordance with maintenance ICS therapy and reduce the likelihood of LABAs being used without ICS." AstraZeneca agrees with this and would also like to highlight that use of a tailored regimen such as Symbicort SMART can potentially increase concordance because the patient no longer requires a SABA (with other combination inhalers a SABA is still used).
Page 24	Here it states that according to Guhan 2000 that both formoterol and salmeterol are relatively well tolerated at

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	recommended doses but their therapeutic window is fairly narrow. AstraZeneca suggests this discussion of the therapeutic window does not accurately reflect the Summary of Product Characteristics (SPC) for formoterol. The SPC for formoterol clearly states that the maximum number of daily inhalation is 12 inhalations of 4.5μg (6μg) within a 24-hour period. AstraZeneca suggests the sentence should be changed to reflect this, e.g. "Both drugs are relatively well tolerated at recommended doses but the therapeutic window of salmeterol is fairly narrow."
Clinical Effectiveness	
Pages XIX, 312, 315, 322, 323, 522	In several places in the TAR, the CONCEPT study (FitzGerald 2005) is assessed without taking into account that the dose of Symbicort is inappropriately low throughout the study. The assessment does not consider that different ways of using the drugs can affect the efficacy and this should be discussed in the text. AstraZeneca suggests the Assessment Group adds the following wording to aid understanding of the trial design: "82% of patients receiving budesonide/formoterol 200/6μg were titrated down to one inhalation per day at some point during the study. Symbicort 200/6μg one inhalation per day represents less than 0.3% of the prescriptions written for Symbicort".
Page 201	On this page it is discussed that the ONLY significant difference between budesonide and beclometasone dipropionate regarding clinical outcomes was exacerbations. As discussed above, from a patients' point of view exacerbations can be frightening episodes that can cause significant morbidity and this statement implies that differences in exacerbations are of no interest to the reader. AstraZeneca suggests that the sentence is rewritten to reflect the importance of exacerbations, for example: "BDP vs BUD (2 RCTs, 1:1 dose ratio) – Significant differences in favour of BUD for exacerbations, otherwise no significant differences." In addition, we suggest to improve clarity a definition of exacerbations should be included in the discussion since the definition varies from trial to trial.

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Pages 215, 216, 234, 299, 300, 303, 304, 333, 438, 439, 566, and 568	AstraZeneca note that within the TAR the term 'single inhaler therapy' is used to refer to combination inhaler therapy. We believe that this term could lead to confusion; it is plausible that it may be interpreted as monotherapy. Therefore, for improved clarity we suggest using the term combination inhaler rather than single inhaler. In addition, on page 438 is there is a section called, "Combination versus single inhaler devices". Using the term 'single inhaler devices' is confusing in this paragraph and inconsistent with the rest of the document. AstraZeneca suggests that the term, 'monocomponents' is used for separate ICS and LABA, and 'combination' is used throughout instead of single inhaler. AstraZeneca suggests the paragraph is changed to: "Combination versus monocomponents There were no consistent differences in the effectiveness of combination ICS plus LABA therapy delivered concurrently compared to delivery in separate inhalers. Cost comparison between the two regimens showed that taking an ICS with a LABA as either of two currently available combination products (Symbicort and Seretide) is cheaper than taking the relevant ingredient drugs in separate inhalers. The use of combination inhaler therapy not only provides a simpler treatment regimen…"
Pages 239	In these pages there are descriptions of the two treatment groups in the Scicchitano *et al* 2004 study (Ref 233). The description for the first group does not clearly explain the treatment. This group is a Symbicort SMART study allowing the BUD/FF dose to be exactly matched to a patient's on-going asthma condition. AstraZeneca suggests the description on page 239 be changed to: "Patients in the first group received ex-actuator doses of 320µg BUD plus 9µg FF per day (metered doses of 400µg and 12µg, respectively). The drugs were delivered via a combined DPI Turbohaler (Symbicort®, Turbuhaler®, AstraZeneca) as two inhalations each evening. This group was a Symbicort SMART group, so the BUD/FF dose could be matched to a patient's on-going asthma condition by varying the number of inhalations. Patients could take up to ten additional inhalations per day as needed."
Page 244	This page contains a table with details of the Scicchitano et al 2004 study (ref 233). The description for the first group does not clearly explain the treatment which is a Symbicort SMART study allowing the BUD/FF dose to be exactly matched to a patient's on-going asthma condition. To make this table consistent with the table summarising the O'Byrne et al 2005 study (ref 232) on page 243, AstraZeneca suggests adding the wording "N.B. This trial also

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	examines the effects of the combination inhaler as a reliever."
Page 245	On this page it describes study treatment arms that could not be included in a meta-analysis because they reflect adjustable dosing. Scicchitano et al 2004 (ref 233) also has a Symbicort SMART treatment arm where the BUD/FF dose can be matched to a patient's on-going asthma condition. AstraZeneca suggests that the sentence is changed to: "Furthermore, in the two studies by O'Byrne and colleagues and Scicchitano et al, one of the treatment arms used the combination inhaler as both maintenance and reliever."
Page 288	It states that there are no differences in adverse events for FP versus FP/SAL, but this effect is less certain for BUD versus BUD/FF. However, on page 281 the summary is that the rate of adverse events, where reported, appeared similar between treatments. AstraZeneca suggests that the summary on page 288 is changed to, "..no difference in adverse events for either FP versus FP/SAL, or BUD versus BUD/FF was found".
Page 300	Here the randomisation and concealment of treatment for the Rosenhall *et al* 2002 trial (ref 246) is discussed. As correctly stated in the summary table of the trial on page 566, this is an open label study so it would not be expected that the treatment allocation be concealed. AstraZeneca suggests that this sentence is removed.
Page 312	Here it states, "Mean baseline FEV_1 was lowest in the patients enrolled into the study by Vogelmeier and colleagues (73%). This suggests mild to moderate asthma, according to guidelines." AstraZeneca would like to point out that for a patient to be eligible for inclusion in the study they had to have used 500 µg/day of budesonide or fluticasone (or at least 1,000 µg of another ICS) for at least 1 month before study entry. This suggests patients are moderate to severe and not mild to moderate. AstraZeneca suggests the sentence is changed to reflect this, e.g. "This suggests moderate to severe asthma, according to guidelines."
Page 316	This page contains a table with details of the Vogelmeier et al 2005 study (ref 248). AstraZeneca has a few comments regarding the table: • In the design column, AstraZeneca suggests that it be made clear this is a trial that looks at the use of Symbicort instead of a separate reliever. This would make it consistent with the table summarising the O'Byrne et al 2005 study (ref 232) on page 243. Suggested wording is, "N.B. This trial also examines the effects of the combination inhaler as a reliever." • In the intervention column it describes the titration for the FP/SAL group. AstraZeneca would like to highlight that the downward titration was from 250/50µg bid to 100/50µg bid and the upward titration was to 500/50µg bid. AstraZeneca suggests the wording is changed to "2. FP/SAL 250/50µg b.i.d. (daily total 500/100µg - titrated up to 500/50µg b.i.d. or down to 100/50µg b.i.d. to improve control + salbutamol relief)".
Pg 319	Here it states, "Aalbers and colleagues did not report use of rescue medication". AstraZeneca would like to highlight that in the Aalbers et al 2004 study (ref 249) it does report the use of medication. The number of inhalations of reliever medication was 1.83 per day during run in the BUD/FF group and 1.76 per day in the FP/SAL group. The mean change

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	after 1 month of treatment was –0.86 in the BUD/FF and –0.81 in the FP/SAL. AstraZeneca suggests the sentence is replaced with: "Aalbers and colleagues reported the use of rescue medication. The number of inhalations of reliever medication was 1.83 per day during run in the BUD/FF group, and 1.76 per day in the FP/SAL group. The mean change after 1 month of treatment was –0.86 in the BUD/FF and –0.81 in the FP/SAL"
Pg 319	On this page it states that the mean number of puffs per day of rescue medication is not reported for the Vogelmeier et al 2005 study. AstraZeneca would like to point out that in the publication (ref 248) it states that over the entire treatment period, patients receiving budesonide/formoterol used 0.58 as needed inhalations per day versus those receiving salmeterol/fluticasone plus salbutamol that required 0.93 inhalations per day. AstraZeneca suggests the sentence is changed to: "Vogelmeier and colleagues reported over the entire treatment period, patients receiving budesonide/formoterol for maintenance plus as needed used 38% less as-needed medication than those receiving salmeterol/fluticasone plus salbutamol (0.58 versus 0.93 inhalations/day; p,0.001)."
Economic analyses	
Pg 345-346	This is a table of studies included in the health economics section. AstraZeneca suggests that the following reference should be added to the health economics section: Price D et al (2004). An economic evaluation of adjustable and fixed dosing with budesonide/formoterol via a single inhaler in asthma patients: the ASSURE study. Curr Med Res Opin. 20(10):1671-9. The cost effectiveness evaluation of this trial demonstrates how efficacy can be improved and cost be reduced by adjusting the maintenance dose of BUD/FF as compared to a fixed maintenance dose regimen with BUD/FF. An important feature of this study is that UK centres were included exclusively.
Page 348 and 349	Here there is a discussion of an analysis to derive utility values from the AQLQ instrument scores. AstraZeneca would like to add that the mapping from non-preference-based instruments to utility values is a technique that is not widely accepted. As such, AstraZeneca suggests this is pointed out in the discussion.
Page 352	Here it states that the GSK model relied solely on symptom-free days for estimates of effectiveness. However, later on the TAR describes on page 381 "the inadequacy of other common trial outcomes, such as lung function or symptom-free days, as a basis for the cost-utility analyses for this assessment." AstraZeneca suggests keeping the discussions of cost-effectiveness models consistent by including this recommendation on page 352.
Page 353	The discussion here is that the model uses health state values of 0.97 for the 'symptom-free' health state, and 0.85 for the 'with symptoms' health state, a utility decrement of 0.12. AstraZeneca would like to point out this is an important

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	assumption implying that utility decrements due to exacerbations are accurately captured within the estimate for the whole 'with-symptoms' state. This would require that the incidence of exacerbations is proportionally related to the time spent with symptoms of any kind, Given the non-transparency of the utility weight derivation it is unclear if this has been demonstrated.
Page 355	On this page there are number of different therapies described and AstraZeneca have a few comments to make on them. Under 'Low dose' the TAR states: "Low dose: FP/SAL 200µg/100µg/day versus BUD/FF 400µg/100µg/day: No CEA - (estimated cost-saving; -£22 to -£183)." AstraZeneca believes that the dose for BUD/FF is incorrect. AstraZeneca suggests the sentence should state: "Low dose: FP/SAL 200µg/100µg/day versus BUD/FF 400µg/12µg/day: No CEA - (estimated cost-saving; -£22 to -£183)" The TAR then moves on to state: "Low dose: FP/SAL 200µg/100µg versus BUD/FF 400µg/200µg/day: No CEA - (estimated cost; -£11 to + £149)." Again AstraZeneca believes that the dose for BUD/FF is incorrect. AstraZeneca suggests the sentence should state: "Low dose: FP/SAL 200µg/100µg versus BUD/FF 400µg/12µg/day: No CEA - (estimated cost; -£11 to + £149)". However, if AstraZeneca's understanding is correct then the two comparisons are the same and so the CEA should be the same. AstraZeneca suggests that this section is checked. In addition, since it is not clear what the comparison is, it is not possible to be confident about commenting on the accuracy of the cost comparisons. Under Medium dose versus high dose the TAR states: "Medium dose versus high dose: FP/SAL 500µg/100µg/day versus BUD/FF 800µg/100µg/day: " The description here does not seem to make sense, given that the two ICS drugs (500µg FP versus 800µg BUD) are in comparable doses according to accepted clinical equivalence. If the descriptions are referring to the LABA components, this should be clarified. In addition, AstraZeneca suggest the dose for BUD/FF is incorrect and should be, "…BUD/FF 800µg/24µg/day". Again since it is not clear what the comparison is, it is not possible to be confident about commenting on the

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	accuracy of the cost comparisons. The TAR then continues: "Medium dose versus low dose: FP/SAL 500µg/100µg/day versus BUD/FF 800µg/200µg/day: CEA – FP/SAL stated to dominate BUD/FF (small cost saving, and very small utility gain (0.0005)) Medium dose versus low dose: FP/SAL MD 500µg/100µg/day versus BUD/FF 800µg/400µg/day: No CEA - (estimated cost-saving; -£18) AstraZeneca believes that the doses for BUD/FF are incorrect, and suggest that the TAR should state: "Medium dose versus low dose: FP/SAL 500µg/100µg/day versus BUD/FF 800µg/24µg/day: CEA – FP/SAL stated to dominate BUD/FF (small cost saving, and very small utility gain (0.0005)) Medium dose versus low dose: FP/SAL MD 500µg/100µg/day versus BUD/FF 800µg/24µgµg/day: No CEA - (estimated cost-saving; -£18) Similar to above, if AstraZeneca's understanding is correct then the two comparisons are the same and so the CEA should be the same. AstraZeneca suggests that this section is checked. In addition, since it is not clear what the comparison is, it is not possible to be confident about commenting on the accuracy of the cost comparisons. The TAR then continues: "High dose versus low dose: fluticaseone/SAL 1000µg/100µg/day versus BUD/FF 1600µg/200µg: No CEA - (estimated cost-saving; -£164 to -£427) High dose versus low dose: FP/SAL 1000µg/100µg/day versus BUD/FF 1600µg/400µg/day: NoCEA - (estimated cost-saving;-£168 to -£431)" AstraZeneca believes that the doses for BUD/FF are incorrect, and suggest that the TAR should state: "High dose versus low dose: fluticaseone/SAL 1000µg/100µg/day versus BUD/FF 1600µg/48µg: No CEA - (estimated cost-saving; -£164 to -£427) High dose versus low dose: FP/SAL 1000µg/100µg/day versus BUD/FF 1600µg/48µg/day: NoCEA - (estimated

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	cost-saving;-£168 to -£431)" Similar to above, if AstraZeneca's understanding is correct then the two comparisons are the same and so the CEA should be the same. AstraZeneca suggests that this section is checked. In addition, since it is not clear what the comparison is, it is not possible to be confident about commenting on the accuracy of the cost comparisons. In the last paragraph on the page it states, "A number of factors are taken into account in the analysis (e.g. dose, price) resulting in a range of cost-effectiveness results". AstraZeneca would like to highlight that only one cost-effectiveness comparison is performed and it should be clarified that all the other results are based on assumptions of clinical efficacy and are not full economic evaluations. In the last sentence on this page it states, "For example, where FP/SAL is said to be dominant when compared to BUD/FF this is based on a very small QALY gain (0.0005)". AstraZeneca would also like to point out that only one clinical trial informed the effectiveness results in this analysis. AstraZeneca suggests the sentence should be rewritten as: "For example, where FP/SAL is said to be dominant when compared to BUD/FF this is based on a very small QALY gain (0.0005) and is based on a single clinical trial."
Page 356 and 357	Within the Critical appraisal checklist of economic evaluation by GSK on page 356 there are a few comments we would like to make: In response to, 'Is effectiveness of the intervention established?' AstraZeneca suggests an assessment of "Partial" is more appropriate. The current assessment is inconsistent with the absence of exacerbations from the model and the "lack of transparency over the calculation of health state utilities". The TAR later describes (page 381) "…the inadequacy of other common trial outcomes, such as lung function or symptom-free days, as a basis for the cost-utility analyses for this assessment." AstraZeneca suggests for consistency with the rest of the document that this should be included in the assessment of the GSK model. For the section, 'Are the costs and consequences consistent with the perspective employed? AstraZeneca again suggests that, for consistency, it should be noted that primary care costs are not included in the model and that the TAR found there to be "a lack of transparency" in the cost calculations and "concerns with the methods used to identify and measure" costs".

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	Under the title, 'Is differential timing considered?' it states, "Nominal 1-year time frame used". AstraZeneca suggests that the "cross-sectional" approach should also be noted here. On page 357 there is a table relating the NICE reference case requirements to the GSK submission. Under the section 'Description of health states for QALY calculations: Use of a standardised and validated generic instrument' AstraZeneca suggests that an assessment of "No" is more appropriate, given that the primary instrument used was the AQLQ (disease-specific questionnaire). The mapping from non-preference-based instruments to EQ-5D is not universally accepted on methodological/theoretical grounds.
Page 359	Here it states, "The general literature available to inform on health state values for asthma is sparse and undeveloped, and whilst the values used for symptom-free in the analysis seems relatively high (compared to some general population age-related values), the important issue is the incremental difference (0.12) used between health state with symptoms and symptom-free." AstraZeneca would like to highlight that there is an implicit issue regarding whether these states accurately capture the utility decrement relating to severe exacerbations. AstraZeneca suggests this point is also discussed here.
Page 361	It concludes that there are, "Concerns over the lack of transparency in estimating health state utilities, and other cost estimates." AstraZeneca would like to add that the mapping from AQLQ used an algorithm that was not given in the paper (acknowledged in TAR, page 167). The mapping from non-preference-based instruments to EQ-5D is not universally accepted on methodological/theoretical grounds. AstraZeneca suggest that these two points are added to the list of concerns.
Page 361	Review of the submission by AstraZeneca (AZ) Here it reads, "The submission states that BUD is the most extensively used ICS…". AstraZeneca would like to point out that in the AstraZeneca submission it states that Budesonide (BUD) is the most extensively **studied** ICS (page 1). AstraZeneca suggests the sentence is changed to: "The submission states that BUD is the most extensively <u>studied</u> ICS, and that 'Pulmicort (budesonide) costs are well within the normal range of costs for maintenance asthma treatments with any ICS' (p32)." On this page it states, "The submission used BUD/FF FD as the base case for cost-effectiveness analysis, working on the basis that BUD/FF AMD and SMART have been shown to be superior to BUD/FF FD". AstraZeneca would like to add that the basis for Symbicort FD as base case is that this treatment represents a common comparator across the Symbicort trial programme. AstraZeneca suggests the sentence is changed to:

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	"The submission used BUD/FF FD as the base case for cost-effectiveness analysis, working on the basis that BUD/FF FD represents a common comparator across the trial programme."
Page 362	Here it states, "The model is developed to capture the difference in exacerbations between comparisons, and the difference in time spent in a non-exacerbation health state". AstraZeneca would also like to highlight that it is important to note that differences in symptom control are also captured in the model, via the use of a reliever inhaler. The model therefore incorporates an asthma control perspective and AstraZeneca suggests the sentence is changed to: "The model is developed to capture the difference in exacerbations between comparisons, the difference in time spent in a non-exacerbation health state, and differences in symptom control." In addition, AstraZeneca would like to highlight that the approach taken in the PenTAG model (Appendix 10) appears to be similar to the AstraZeneca approach, although no discussion is provided in the TAR. AstraZeneca suggest that the similarity between the two approaches is included in the discussion on this page.
Page 363	It states, "Primary care NHS resource use (consultations) are assumed to be the same for each of the treatment options, and are not included in the model". AstraZeneca would like to highlight that primary care attendances related to exacerbations are included in the model. Ongoing patient review meetings were not included as they were assumed to be regular and equivalent for all treatment strategies. AstraZeneca suggests the sentence is changed to: "Ongoing Primary care NHS consultations are assumed to be the same for each of the treatment options, and are not included in the model. However primary care attendances related to exacerbations are included in the model."
Page 363	Here it states, "Equivalence in effect was assumed when compared to ICS plus LABA separates". AstraZeneca would like to point out that this assumption is in accordance with the NICE scope which stated that comparison with separates would be on a cost basis only. AstraZeneca suggest the sentence is changed to: "As instructed in the NICE scope, equivalence in effect was assumed when compared to ICS plus LABA separates".
Page 364 and 365	Under the heading, 'Has the correct patient group / population of interest been clearly stated?' the checklist states "Partial". AstraZeneca suggests that an assessment of "Yes" is more appropriate. Patients in the model may be 'uncontrolled' to some extent, i.e. they may start with symptoms. This is because the non-exacerbation state is divided between time with and without reliever use, representing presence or absence of symptoms, respectively. In practice, very few patients would be in a state of exacerbation at any one point, given that, typically, a severe exacerbation persists for about one week.

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	Under the heading 'Is the correct comparator used?' it states "Partial". AstraZeneca suggests that an assessment of "Yes" is more appropriate. Other comparators are included on a clinical equivalence basis, i.e. incorporated into expected costs only. Also, the current assessment is inconsistent with that within the paediatric TAR and that of the GSK model. For the section, 'Is the perspective employed appropriate?' it states for outcomes "Partial". AstraZeneca suggests that an outcomes assessment of "Yes" is more appropriate. Differences in asthma symptom control are captured in the model, via the time spent with/without use of a reliever inhaler. The TAR elsewhere states (page 33), "A key indicator of poor symptom control is a greater frequency of use of reliever medication". A cost-utility approach, utilising a global quality of life measure, by definition focuses on all health effects impacting on patients. For the section, 'Is effectiveness of the intervention established?' it states "Partial". AstraZeneca suggests that an assessment of "Yes" is more appropriate. The current assessment is inconsistent with the GSK model as the CEA is based on a systematic review and meta-analysis of data relating to Symbicort, and is driven by both exacerbation and symptom data, as is elsewhere recommended by the TAR. Under the heading, 'Are the costs and consequences consistent with the perspective employed?' it states "Partial". AstraZeneca suggests that the costs and consequences in the model are aligned with the NHS perspective required. Note that the TAR elsewhere (page 34) states that, "Asthma exacerbations (or asthma "attacks") are one of the key acute events which lead to the consumption of additional medications, or to patient-initiated health care consultations. They are also the likely cause of the more expensive types of asthma-related health care use, such as A & E attendances and hospital admissions."
Page 366	NICE reference case requirements – AZ submission For the section, 'Perspective on outcomes: All health effects on individuals' it states "Partial". AstraZeneca suggests that an assessment of "Yes" is appropriate. Adverse events and mortality were not included in the model when no significant differences were apparent in a systematic review of the clinical trial programme. Exacerbations and use of reliever inhalers were the key drivers of the model, as recommended elsewhere by the TAR. A global quality of life measure was employed. For the section, 'Description of health states for QALY calculations: Use of a standardised and validated generic

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	instrument' AstraZeneca would like to comment that the AstraZeneca study more closely matches NICE requirements than the Dewilde study. The Dewilde study (used in the PenTAG model) uses three different methods and two different populations to derive utilities for the model's health states (similar to the AstraZeneca model health states), which reduces the internal validity of the estimates. In addition, one of the methods used involves the mapping from a non-preference-based measure to a preference-based measure, a method neither widely accepted nor proven. Under the heading, 'Method of preference elicitation for health state values: Choice-based method (e.g. TTO, SG, not rating scale)" it states "Partial". AstraZeneca suggests that an assessment of "Yes" is more appropriate. The method of preference elicitation was described and was choice-based. UK population health state valuations, collected using TTO methods (Dolan et al., 1995) were applied to the EQ-5D classifications chosen by study respondents for the model health states. The current assessment is inconsistent with the TAR stating (page 368) that "data on health state utilities are consistent with the preferred approach of NICE".
Page 366	Here it states, "Trial data have been used to estimate the transition probabilities between these states (and treatment change), but it is unclear how data may have been interpreted from different clinical trials, where methods may not have been homogeneous". AstraZeneca would like to highlight that details of the methods of the clinical trials were provided in the AstraZeneca submission and are available in the publications. The rationale and methods of combining clinical trials were fully reported in the meta-analysis section of the submission and as such AstraZeneca suggests the sentence is changed to: "Trial data have been used to estimate the transition probabilities between these states (and treatment change). Details of the methods of the clinical trials are available in the publications and the rationale and methods of combining the clinical trials were fully reported in the meta-analysis section of the submission." It also states, "For the non-exacerbation state the correlation with trial data is around controlled and symptom-free days". The correlation to trial data is based on days with and without reliever use and the terms "controlled" and "symptom-free" can have many meanings, depending on the clinical trial in question. As such AstraZeneca suggests that the sentence is changed to: "For the non-exacerbation state the correlation with trial data is based on days with and without reliever use".
Page 367	Here the report states, "Much of the data to inform the model transitions have been taken from a limited evidence base, with citations to unpublished data on file at AZ". AstraZeneca would like to highlight that patient-level data are usually unpublished by manufacturers, although all the clinical trials have been publicly reported.

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	Here it also states, “The model structure is not discussed and justified in the context of a coherent theory of asthma, and the model is essentially based around the availability of data surrounding exacerbations for BUD/FF and comparators. It may be that AZ have adopted this approach due to the more positive profile of BUD/FF (against exacerbation rates), when use of an outcome related more directly to control, such as percentage of symptom-free days, may have seemed more favourable for comparator products (e.g. FP/SAL).” AstraZeneca would like to highlight the statement on page 34 of the TAR, which states, "Asthma exacerbations (or asthma ‘attacks’) are one of the key acute events which lead to the consumption of additional medications, or to patient-initiated health care consultations. They are also the likely cause of the more expensive types of asthma-related health care use, such as A & E attendances and hospital admissions." Since exacerbations are of key importance to patients and clinicians alike, they were used as the primary endpoint in the AZ asthma trials. In using these trial data in the model, AZ merely employed the primary endpoint, that of exacerbations, as the basis of the model. The implication of this statement in the TAR is that the trials used exacerbation rates as primary endpoints because Symbicort would look better than Seretide. AstraZeneca would like to highlight that the outcome of the trial could not be known before the trial was started. In addition, AstraZeneca would like to highlight that a symptom-based measure, proportion of reliever-use-free days, did inform the model, as described previously. AstraZeneca suggest the two sentences are removed or amended to reflect these points. In addition, as stated above AstraZeneca would like to highlight that the approach taken in the PenTAG model (Appendix 10) appears to be similar to the AstraZeneca approach, although no discussion is provided in the TAR. AstraZeneca suggest that the similarity between the two approaches is included in the discussion on this page. It also states: “However, treatment effect is based primarily on 12-week trial data (ASSURE Trial), and the submission does not discuss the assumption that this treatment effect is assumed to continue for the time period of the model (1-year in base case), nor the generalisability of the trial data (importantly that from the BUD/FF trial used for transition probabilities) to the broader treatment population.”

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	AstraZeneca would like to clarify that in the submission it stated that the ASSURE trial was the only trial for which patient-level data was available to AstraZeneca UK. In addition, the trial was UK based and hence most relevant to the current appraisal.
Page 368	Here it states, "There is also no statement in the submission on the evaluation of the internal consistency of the model". AstraZeneca would like to point out that whilst this wasn't noted in the AZ submission the model was evaluated for estimated outcomes compared to actual outcomes observed in the ASSURE trial over 12 weeks. The evaluation demonstrated the internal validity of the model and as such AstraZeneca suggests the sentence is removed. It also states, "For effectiveness data, as above, the transition probabilities are estimated from a limited evidence base (BUD/FF FD arm of one RCT), and there is a lack of transparency over the calculation of relative treatment effect for comparator products". AstraZeneca would like to highlight that the synthesis of trial data via meta-analysis was fully reported in the submission. All treatment effect relative risks for comparators, which were applied to the baseline transition probabilities of Symbicort FD, were presented in the submission. As such AstraZeneca suggests the sentence is changed to: "For effectiveness data, as above, the transition probabilities are estimated by applying relative risks estimated in the meta-analysis to the baseline transition probabilities, as reported in the submission. Details of the methods of the meta-analysis were also given in the submission."
Page 369	Here it states, "However, although the choice of distributions would seem to follow accepted methods, in many cases the uncertainty around parameter inputs is very small". AstraZeneca would like to highlight that the sources of variability in the data were reported in the submission, e.g. number of inhalations were drawn directly from the Clinical Study Reports. The sizes of the ranges were not dictated by AstraZeneca but by actual data. It states here, "…the report refers to the use of probabilistic methods for transition probabilities, however it is unclear how the probabilities were sampled (either re-scaled to sum to 1.00, or via some correlation matrix; the submission states "normalised to give a sum of one "p99")." AstraZeneca would like to clarify that the probabilities were re-scaled to sum to 1 and as such suggests the sentence is changed to: "the report refers to the use of probabilistic methods for transition probabilities, the probabilities were re-scaled sampled to sum to 1.00," The TAR reports, "The assessment of uncertainty does not address any issue of heterogeneity in the treatment group,

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	and certain structural and methodological uncertainties are not addressed in the sensitivity analysis (e.g. impact of exacerbations on patients)." AstraZeneca are unaware of any specific heterogeneity within moderate/severe asthma patients requiring inhaled corticosteroids for which subgroup evidence is available and suggests that this criticism is removed from the TAR. Here it states, "The deterministic analysis presented indicates very large changes in the cost per QALY results when assumptions over the proportion of time without SABA used are considered". AstraZeneca would like to clarify that this relates to reliever use and not SABA use. We suggest the sentence is changed to: "The deterministic analysis presented indicates very large changes in the cost per QALY results when assumptions over the proportion of time without reliever used are considered". It states here, "There is the use of a limited evidence base to populate the model i.e. the arm of one RCT used to estimate the transition probabilities for BUD/FF." AstraZeneca followed the recommended NICE approach by using a systematic review and meta-analysis to inform the clinical evidence used in the model. In addition, the baseline transition probabilities are from patient-level data gathered in a UK trial, and so is one that is most relevant to an NHS perspective. As such, we suggest this sentence is changed to: "As recommended by NICE a systematic review and meta-analysis were to inform the clinical evidence used in the model. In addition, the baseline transition probabilities were taken from patient-level data gathered in a UK trial, and so one that is most relevant to an NHS perspective." It reports here that, "The lack of transparency over the estimation of relative treatment effect (unpublished, 'in confidence' data cited)." AstraZeneca would like to point out that the meta-analysis was fully reported in the submission but has not yet been published. It was therefore necessary to protect this work with confidentiality designation until publication. AstraZeneca suggests the sentence is removed from the TAR. In addition, the results of the AstraZeneca model are corroborated by those of the PenTAG model presented in Appendix 10, which adds external validity to the findings. AstraZeneca suggest that the similarity between the two approaches and this external validity of the results of the AstraZeneca model are included in the discussion on this page.

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Page 378	It states here, "Moreover, the methods used for estimating the product costs varied across the submissions, and were not transparent." The full calculations were presented in an appendix to the AstraZeneca submission and as such we suggest that the sentence is removed.
Page 381	On this page it states, "…considerable uncertainty surrounding the model outputs; in particular the sensitivity of central estimate ICERs to very small changes in effectiveness and medication cost assumptions relating to the controlled asthma state." In the base case and under reasonable sensitivity assumptions (see further notes in Appendix 10), some reliance could be placed upon the model estimates. AstraZeneca suggests this sentence is removed and the results from the base case and sensitivity analysis be brought forward into the main body of the report.
Page 381, 384 and 385	The final sentence of page 381 states, "More often instead, there is inconclusive evidence concerning differential effectiveness." We feel that this does not provide a justification for using cost comparison. It is not a recognised method of full economic evaluation because it takes into account costs only and not effectiveness. Lack of effectiveness data may help to explain the absence of an economic evaluation but does not support the use of cost evaluation only. In addition, AstraZeneca suggests the comments by the assessment group on Page 384 cast doubt on the usefulness or validity of this type of cost comparison. On page 385 it states "However, to perform a cost comparison on the basis of a basic assumption of equivalent effectiveness". AstraZeneca would like to point out that equivalent efficacy has not been demonstrated and cost comparison as a method is usually considered of low validity. AstraZeneca suggest that more emphasis is placed on these limitations in the introduction, rationale and results within section 6 of the TAR. In addition, AstraZeneca would like to highlight that there is a cost-utility model in Appendix 10 and suggest this should be mentioned throughout the main body of the TAR.
Page 405	Here it discusses cost-consequence comparison. AstraZeneca would like to add that a cost-consequence analysis does not evaluate cost-effectiveness. We suggest the sentence, "They therefore still only offer a limited perspective on our original, broader, cost-effectiveness question." is changed to: "In addition, cost-consequence analysis does not evaluate cost-effectiveness. In summary, therefore they still only offer a limited perspective on our original, broader, cost-effectiveness question."
Page 408	The final sentence states, "At this higher dose level currently available BUD preparations cost on average £225 per year; only slightly less expensive than MF." AstraZeneca suggests the second part of this sentence is unnecessary since the current acquisition cost is already given. AstraZeneca suggests the sentence is changed to:

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	"At this higher dose level currently available BUD preparations cost on average £225 per year."
Page 409	It states here, "This is an issue particularly for BDP, BUD and FP products". The text then continues to give examples for BDP and BUD. AstraZeneca suggests that in the interest of completeness an example for the third drug, FP should also be given. AstraZeneca suggests the following is added: "Similarly, for obtaining 500µg of FP per day, the cheapest product is Flixotide Evohaler® FP 250µg taken twice daily (60p per dose = £219.85 per year); the most expensive product is Flixotide Diskhaler® FP 250µg taken twice daily (80p per dose = £293.34 per year)."
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Page 427	Here it states, "The scope does, however, include the use of ICS and LABA in a combination inhaler compared to the two in separate inhalers." AstraZeneca would like to add that the scope states that the comparison would be made on a cost basis only. AstraZeneca suggests that the sentence is revised to: "The scope does, however, include the cost comparison of ICS and LABA in a combination inhaler compared to the two in separate inhalers. Comparison of effectiveness is, however, beyond the scope."
Page 428	The last paragraph describes the EXCEL study (Dahl et al 2006). In the paragraph it states that the study's "…methodology and findings have not formally been assessed". AstraZeneca suggests that until the study methodology has been assessed that this study is removed from the TAR and this paragraph deleted.
Page 434	Here it states, "Conversely, evaluations dominantly based on exacerbations as an outcome, including the exploratory analysis carried out as part of this report, may not fully reflect differences in costs and utility associated with varying levels of 'non-exacerbation' asthma control." AstraZeneca would like to again highlight that the model submitted did capture varying levels of "non-exacerbation" control via time with/without reliever use and the costs/utility differences associated with these two states. AstraZeneca suggest the discussion is changed here to reflect this.
Appendices	
Page 576	In the table of details of the Vogelmeier et al 2005 study it states, "Average daily microgram ICS dose was similar between the two groups over the treatment period, Group A =562µg (maintenance) + 91µg (as-needed) vs Group B 583µg (maintenance only). Corresponding values expressed as beclometasone dipropionate (BDP) doses were 1,019µg/day^{-1} (Group A maintenance and as needed) vs 116µg/day^{-1} (Group B maintenance only)". AstraZeneca would like to highlight that when the doses are converted into BDP, Group B should be µg/day^{-1}, and Group B should be

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	1166µg/day^{-1}. AstraZeneca suggest the statement should be changed to: "Average daily microgram ICS dose was similar between the two groups over the treatment period, Group A =562µg (maintenance) + 91µg (as-needed) vs Group B 583µg (maintenance only). Corresponding values expressed as beclometasone dipropionate (BDP) doses were 1,019µg/day^{-1} (Group A maintenance and as needed) vs 1166µg/day^{-1} (Group B maintenance only)"
Page 583	APPENDIX 5 In this appendix is a list of studies from updated literature search to be included in any future update of the assessment report. AstraZeneca notes that the cut-off date for literature to be included is October 2006. In this list of studies is Jenkins C, Kolarikova R, Kuna P, Caillaud D, Sanchis J, Popp W et al. Efficacy and safety of high-dose budesonide/formoterol (Symbicort) compared with budesonide administered either concomitantly with formoterol or alone in patients with persistent symptomatic asthma. Respirology 2006;11:276-86. AstraZeneca would like to clarify this was published in May 2006 and should therefore be included in the 'updated literature search' section. Similarly, Rabe KF, Pizzichini E, Stallberg B, Romero S, Balanzat AM, Atienza T et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma - A randomized, double-blind trial. Chest 2006;129:246-56. This study was published in Feb 2006 and again should be included in the 'updated literature search' section.
Page 617	Here it states, "Briggs and colleagues do not provide information on the mapping algorithm used (which remains unpublished), with the only explanation of methods being cited as a personal communication with the research team responsible for the algorithm. Briggs and colleagues used the data mapped to utility scores to undertake regression analysis that allowed utility scores to be associated with the asthma control status observed in the trial." AstraZeneca would like to suggest that since the algorithm is not provided for validation and the mapping of non-preference-based instruments to utility scores is not thoroughly supported as a methodology, that these limitations with respect to the GSK model should be discussed at the end of the first paragraph on page 618.
Page 618	Here it states, "From the three studies identified in the present review, Briggs and colleagues (2006) report a difference (increment) of 0.104 between asthma health states of 'total control' and 'not well controlled'". These increments are consistent with those in the AstraZeneca utility study and we feel this should be reflected in the text on p368.
Page 620	APPENDIX 10 – The PenTAG asthma model

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	In this section the model structure is presented. AstraZeneca would like to highlight that this structure is similar to that of the AstraZeneca model and that this similarity should be acknowledged in the assessment of the AstraZeneca model (pages 362, 366, and 367 of the TAR).
Page 621	Here it states, “Half-cycle correction was not applied to the outputs at each cycle since it is not relevant for such a short cycle length”. AstraZeneca suggests that the cycle length is reported here.
Page 622	It states here, “Many of these assumptions drew on patient administration data from the Royal Devon and Exeter Hospital, Exeter, and the Southampton University Hospital, Southampton, supplemented by expert advice where no other data were available”. AstraZeneca suggests that to maintain transparency in the TAR it would be useful to provide the justification regarding use of this cost evidence’. In addition, a statement of how these costs were validated and the demonstration of how representative they are for the UK should be provided.
Page 624	In the table (TABLE A10.3 Model inputs (BUD/FF v higher-dose ICS): Transition probabilities) AstraZeneca suggests that the second-line ICS regimen should be defined. In addition, the Assessment Group should clarify if this is a higher steroid dose than the first-line regimen? If it is not, then patients are moving on to a less efficacious regimen. Also, the source of this input (proportion changing to ICS only) should be stated.
Page 625	On this page it states, “The plot reveals the wide spread of outputs caused by the parameter uncertainty in the model”. AstraZeneca suggests that the wording of this sentence is changed to reflect the observation that the great majority of simulations fall in the two quadrants associated with QALY gains for BUD/FF over ICS alone, e.g. “The plot reveals the wide spread of outputs caused by the parameter uncertainty in the model, but the majority of simulations fall in the two quadrants associated with QALY gains for BUD/FF over ICS alone.”
Page 627	It reports here, “This analysis shows the extreme sensitivity of model outputs to any differential utility between the arms in the controlled asthma state. The importance of this variable in determining the cost-effectiveness of an intervention in this context illustrates the potentially major impact of quality-of-life improvements for asthma patients in periods without exacerbations.” AstraZeneca agrees and would like to point out that this is also apparent in the AstraZeneca model. It should also be noted that BUD/FF consistently shows a statistically significant difference in time without symptoms in the controlled asthma state, proxied by reliever use, compared to ICS alone. It therefore seems likely that BUD/FF is as or more cost-effective than in the base case shown here.
Page 628	Here it states, “The effect of changes to costs in the Controlled Asthma state for FP/S were examined using a differential factor applied as a fixed multiplier for the sampled cost value for each simulation. This analysis generated the array of CEACs shown in Figure A10.5.” AstraZeneca would like to add, that given that asthma is "controlled" in this state, and the cost of a reliever inhalation is approximately £0.07 (compared to base case cycle cost of approximately £4), it seems unlikely that costs would vary so much in the controlled state.

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Page 631	It reports here, "This shows that at a WTP of £20,000 per QALY the probability that BUD/FF is cost-effective is less than a third, at £30,000 it is about 38% and the probability does not exceed 50% until the WTP value is over 65%." AstraZeneca believes that BUD/FF should be FP/S here and suggests that the sentence should read: "This shows that at a WTP of £20,000 per QALY the probability that FP/S is cost-effective is less than a third, at £30,000 it is about 38% and the probability does not exceed 50% until the WTP value is over 65%. "
Page 633	It states here, "This means that, if FP/S could be shown to provide a day-to-day utility gain of 0.73 quality-adjusted days per year or more, we would expect it to appear cost-effective in our model." AstraZeneca suggests this discussion of the CEACs and the probability that the combination is cost-effective is missing from the BUD/FF vs. ICS alone analysis (Page 625) where probabilities appear to be higher. AstraZeneca suggests that to be consistent, a similar statement should be added to p625 or the sentence should be removed from here.
Page 636	In the table (TABLE A10.9 Model inputs (FP/S v BUD/FF): Transition probabilities) the trials used to inform these probabilities have not been stated. It would be useful for the reader if these were added.
Page 637	On this page it states, "The mean value reflects the deterministic output of very little differential between arms in terms of effectiveness, coupled with an apparent cost advantage in favour of BUD/FF." AstraZeneca would like to add that BUD/FF is also shown here to be marginally more effective. AstraZeneca suggests the sentence should be changed to: "The mean value reflects the deterministic output of very little differential between arms in terms of effectiveness, however, there is an apparent efficacy advantage of BUD/FF coupled with an apparent cost advantage in favour of BUD/FF." It also states, "The CEAC is plotted below. This charts the probability that FP/S will be found to be costeffective for a range of WTP thresholds." AstraZeneca would like to point out the CEAC shows that BUD/FF is expected to be cost-effective across all possible willingness-to-pay thresholds. AstraZeneca suggests the sentences are changed to reflect this, e.g.: "The CEAC is plotted below. This chart shows that BUD/FF is expected to be cost-effective across all possible willingness-to-pay thresholds."
Page 639	Here it discusses the probabilistic analysis of costs in the controlled asthma states. AstraZeneca would like to comment that it seems unlikely that costs in the controlled state would vary so much given the low cost of reliever medication. AstraZeneca suggests this is highlighted in the discussion.
Page 641	On this page it states, "Model Dynamics: The parameters of the controlled asthma state, where approximately 90% of

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	population state occupancy resides during the one year model time horizon, are predominant in determining outputs." AstraZeneca would like to comment that this is also reflected in the AstraZeneca model and could be given more consideration in the discussion of suitable effectiveness outcomes for the PenTAG model, as well as the assessment of the manufacturer models. Another observation is that the base case results of the PenTAG model corroborate those of the AstraZeneca model. AstraZeneca suggests that this is added to the summary here.
Other comments and Typographical errors	
	Generally in the TAR, AstraZeneca is referred to as AstraZeneca or AZ. In a few places (pg 338, 350, 361, and 378) Astra-Zeneca is used, please can you change this to AstraZeneca or AZ.
Page 20	On page 20 of the report, a study by Todd 2002 is described. This study reported the frequency of adrenal crisis associated with ICS in 2912 people. 33 cases of adrenal crisis were identified. Of these 30 had received FP, 1 FP and BUD, and 2 BDP. After each figure the percentage is also given. For FP this is stated as 30 people or 1%, where as for BDP it states 2 people or 6%. AstraZeneca suggests that there is a typo and the percentage for FP should be 91%, and suggest the text should be: "Of these 33 patients who had received ICS in the range of 500-2000µg per day, 30 <u>of the 33 (91%)</u> had received FP, one (3%) FP and BUD, and two (6%) BDP."
Pages 242, 256, 257, 287, 404, 557, and 558	On these pages it describes the use of "adjustable dose maintenance" or "ADM". AstraZeneca would like to point out that as stated elsewhere in the TAR the description should be "adjustable maintenance dose" or "AMD"
Page 243	This page contains a table with details of the O'Byrne et al 2005 study (ref 232). AstraZeneca has a few points regarding the table: • In the intervention column where it details the treatment for the first group it states "1. BUD/FF 80µg/4.5µg b.i.d. plus 80µg/4.5µg as needed (daily total 160µg/9µg) + combination inhaler as reliever" it appears to repeat the reliever medication. AstraZeneca suggests it is revised to: "1. BUD/FF 80µg/4.5µg b.i.d. <u>(daily total 160µg/9µg) plus combination inhaler as reliever</u>" • In the intervention column it also incorrectly states treatment groups 1, 2 and 3 received Pulmicort Turbuhaler®. We suggest this should be changed to state that treatment groups 1 and 2 received Symbicort Turbuhaler®. • In the outcomes column, AstraZeneca suggests it should also include, "<u>Severe exacerbations requiring medical</u>

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	attention". This would make it consistent with the details for other studies in the TAR, e.g. Scicchitano et al (2004) (pg 244). • In addition, we believe that in the table it should reflect that the children in the trial (age 4-11 years) received half the maintenance dose to adults.
Page 272	In the text it states, "The trial by Kuna and colleagues tested similar regimens, but with higher doses." This is contrasting the Buhl et al 2003 (ref 241) and Kuna et al 2006 (ref 242) studies. In Buhl et al 2003 the treatment dose is higher than in Kuna et al 2006. AstraZeneca suggests the sentence should be changed to, "The trial by Kuna and colleagues tested similar regimens, but with lower doses."
Page 273 and 299	On page 273 it states, "An inhalation of BUD/FF 160µg/4.5µg from the combination inhaler delivers the same quantity as a 200µg metered inhalation of BUD and as a 4.5µg metered inhalation of FF". AstraZeneca would like to highlight that the 4.5µg is the delivered dose of FF, the metered dose is 6µg of FF. The sentence should be changed to: "An inhalation of BUD/FF 160µg/4.5µg from the combination inhaler delivers the same quantity as a 200µg metered inhalation of BUD and as a 6µg metered inhalation of FF". Similarly on page 299 it states, "An inhalation of BUD/FF 160µg/4.5µg from the single inhaler (Symbicort® Turbuhaler®, AstraZeneca) delivers the same quantity as a 200µg metered inhalation of BUD (Pulmicort Turbuhaler®, AstraZeneca) and a 4.5µg metered inhalation of FF from separate inhalers." Again AstraZeneca asks that this be changed, also as discussed above the term single inhaler is confusing and AstraZeneca suggest combination inhaler should be used. AstraZeneca suggest the text is changed to, "An inhalation of BUD/FF 160µg/4.5µg from the combination inhaler (Symbicort® Turbuhaler®, AstraZeneca) delivers the same quantity as a 200µg metered inhalation of BUD (Pulmicort Turbuhaler®, AstraZeneca) and a 6µg metered inhalation of FF from separate inhalers."
Page 362	In the 6th and 29th line formoterol is spelt formoaterol. Also on the 29th line formoterol is spelt formoteraol.