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**Single Technology Appraisal (STA)**

**Ciclosporin for treating dry eye disease ID665 – response to clarification questions**

Dear Frances,

Please find below Santen's responses to the clarification questions voiced by Liverpool Reviews and Implementation Group (LRiG) for your consideration. A CD with the additional references requested has been couriered directly to LRiG.

Yours sincerely,

Fredric Ernst

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**Section A: Clarification on effectiveness data**

**Literature searching**:

| | | Response |
|---|---|---|
| A1. | **Priority question: Previously published systematic reviews.** Two systematic reviews by Sacchetti 2014 [British Journal of Ophthalmology; 98(8):1016-22] and Zhou 2014 [Cornea; 33(7):760-7] have been recently published. In total, these two reviews included 20 RCTs. | |
| | i. Please clarify if the company's search identified these systematic reviews. | We did not conduct a search for systematic reviews therefore these sources were not identified. |
| | ii. Please clarify if the company considered the studies included in these reviews for inclusion. | If studies met the inclusion criteria for the systematic review of clinical efficacy conducted they were considered for inclusion. |
| | iii. Please provide the rationale for the exclusion of each trial included in these reviews in Table A1 below. | Rationale provided below. For those studies included in our systematic review rationale for not discussing studies further in the submission is provided in the submission. |

***Table A1: Ciclosporin trials excluded from evidence synthesis in company's submission***

| Study | Source | Reason for exclusion |
|---|---|---|
| Altiparmak 2010 | Eye; 24:1044-50 [Erratum appears in 26(12):1602] | Patients not considered severe according to the definition of severe in the SANSIKA trial: 'Patients with a BUT of <10 s and Schirmer's test of <10mm were considered as dry eye and were included in the study' |
| Baiza-Duran 2010 | British Journal of Ophthalmology; 94:1312-5 | Reporting of outcomes.<br>With the exception of the Schirmer test, outcomes were reported a p-values and there reporting was considered insufficient. The Schirmer test conducted was with anaesthetic; our eligibility criteria specified that only Schirmer tests without anaesthetic would be considered. |
| Chen 2010 | Journal of Ocular Pharmacology & Therapeutics; 26:361-6 | Reporting of outcomes. 'The severity of these symptoms was graded using a 5-point scale: 0=no symptoms, 1=mild, 2=moderate, 4=severe, 5=profound'; all outcomes were reported using this scale which is not consistent with the reporting observed in other trials. Our systematic review protocol specified accepted units for reporting. |
| Demirya y 2011 | Eye and Contact Lens; 37:312-5 | Patients not considered severe according to the definition of severe in the SANSIKA trial: 'The inclusion criteria for the study were Schirmer-I (without anaesthesia) scores below 10 mm/5 min and tear film break-up time (BUT) below 10 sec as defined for mild to severe patients with DTS in the DEWS grading scheme.' |
| Gündüz 1994 | Acta Ophthalmologica ; 72:438-42 | Patients not considered severe according to the definition of severe in the SANSIKA trial: mean Schirmer-I and TBUT at baseline were both >5. |

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| Study | Source | Reason for exclusion |
|---|---|---|
| Guzey 2009 | Clinical & Experimental Ophthalmology; 37:541-9 | Study enrolled patients with 'severe trachomatous dry eye'. This is a chronic contagious infection of the cornea caused by *Chlamydia trachomatis* These patients are not considered to have DED |
| Jain 2007 | Annals Of Ophthalmology; 39:19-25 | Study was excluded at abstract review stage of systematic review as the title and abstract appear to report a single arm trial. Having looked at the study it would not have been included in the systematic review anyway - patients are not considered severe according to the definition of severe in the SANSIKA trial: 'tear-film break-up (TBUT) of less than 10 seconds, Schirmer test-I scores less than 8 mm/5 minutes' |
| Kim 2009 | American Journal of Ophthalmology; 147:206-13.e3 | Included in systematic review |
| Laibovitz 1993 | Cornea; 12:315-23 | Patients not considered severe according to the definition of severe in the SANSIKA trial: 'For the purposes of this study, keratoconjunctivitis sicca was defined as a syndrome of ocular surface changes with moderate to severe symptoms of dry eyes. As evidence of ocular surface changes, patients were required to have positive Rose Bengal staining with a score of> 3 in at least one eye using the van Bijsterveld method (28). Patients also had to have one or more of the following symptoms, graded at least moderate in severity: itching, tearing, blurred vision, burning, foreign body sensation, redness, sensitivity to light, or mucous production. Both symptoms and objective signs must have been present despite conventional management for dry eye.' |
| Liew 2012 | Ophthalmology; 119:1328-35 | Patients not considered severe according to the definition of severe in the SANSIKA trial: (1) Schirmer wetting test without anesthesia results of 1 mm or more and 7 mm or less per 5 minutes; (2) corneal fluorescein staining total score of 4 or more according to the National Eye Institute Industry/Workshop Scale16 (a micropipette was used for corneal staining with fluorescein); and (3) a score of at least 3 (0–6 scale) on 4 of the 16 questions in the Ocular Comfort Index (OCI) |
| Moon 2007 | Korean Journal of Ophthalmology; 21:189-94 | Not an RCT |
| Rao 2010 | Journal of Ocular Pharmacology & Therapeutics; 26:157-64 | Patients not considered severe according to the definition of severe in the SANSIKA trial: 'Disease severity was assessed according to the ITF consensus guidelines […] The mean baseline Schirmer test score was 7.7 ± 0.6 mm in patients randomized to artificial tears and 7.9 ± 1.2 mm in patients randomized to cyclosporine 0.05% [...] The mean baseline TBUT was 5.0 ± 0.8 s in patients randomized to artificial tears and 4.9 ± 0.8 s in patients randomized to cyclosporine 0.05% […] Patients randomized to artificial tears or cyclosporine 0.05% had similar OSDI scores at baseline (19.1 ± 1.9 and 18.9 ± 2.9, respectively' |
| Rao 2011 | Journal of Ocular Pharmacology & Therapeutics; 27:603-9 | Follow-on to Rao 2010 [duplicate patient population] |
| Salib 2006 | Journal of Cataract & Refractive Surgery; 32:772-8 | Patients received LASIK halfway through the study; LASIK was an exclusion criterion for the Ikervis trials and therefore any studies including LASIK patients were excluded. |

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| Study | Source | Reason for exclusion |
|---|---|---|
| Sall 2000 | Ophthalmology; 107:631-9 [Erratum appears in 107(7):1220] | Included in systematic review |
| Sall 2006 | Eye and Contact Lens; 32:21-6 | Patients not considered severe according to the definition of severe in the SANSIKA trial:' To be eligible for inclusion, patients had to express a desire to use eye drops at least "some of the time" and have a National Eye Institute sodium fluorescein corneal staining score of 3 or more (five zones on a 0-to-3 scale with 15 points possible) at the screening visit (day -7) in one eye and again at the eligibility visit (day 0) in the same eye. In addition, patients must have had a Schirmer I score of 7 mm or less without anesthesia at day -7' |
| Schrell 2012 | Klinische Monatsblatter fur Augenheilkunde; 229:548-53 | All outcomes were reported as medians; we only included studies which reported outcomes as means. |
| Stevens on 2000 | Ophthalmology; 107:967-74 | Included in systematic review |
| Su 2011 | Cornea; 30:1098-104 | The study reported that the majority of patients had moderate DED: 'Forty-five patients had mild dry eye disease. Thirty-eight patients had moderate disease. Seventeen patients had severe disease.' |
| Willen 2008 | Eye and Contact Lens; 34:43-5. | Patients included were not DED patients - patients were recruited if they wore contact lenses and had reported dry eye problems. |

| | | |
|---|---|---|
| A2. | Please clarify whether you have tried to contact the authors regarding the findings of the ongoing systematic review currently being conducted on behalf of the Cochrane Collaboration (protocol available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010051/abstract). | We have not tried to contact the authors of the ongoing Cochrane Collaboration systematic review. |
| A3. | Pages 39 and 221 of the company's submission appear to imply only part of the Cochrane Library was searched (i.e. CENTRAL). Please confirm if this was the case and if so, clarify why the whole of the Cochrane Library was not searched. | The purpose of the systematic review of clinical efficacy was to identify randomised controlled trials of DED patients. The Cochrane Central Register of Controlled Trials is the only database provided by the Cochrane Library which includes randomised controlled trials and therefore it was appropriate to only search CENTRAL. |

| **Clinical-effectiveness data:** | | Response |
|---|---|---|
| A4. | **Priority question: Ciclosporin (Ikervis) formulation.** The company's submission notes that different formulations of ciclosporin in olive or castor oil exist and these may be administered up to four | |

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| times daily. | |
| i. Notwithstanding reasons for exclusion (see response to question A1), does the company consider that data from trials of different formulations and from different manufacturers of these ciclosporin formulations can be pooled? | We do not consider that data from trials of different formulations and from different manufactures of ciclosporin could be pooled. There are two main reasons for this:<br>• The 0.05% ciclosporin used in Restasis has not been licensed in Europe; the Ikervis formulation has received its European license<br>• The vehicle used for ciclosporin by different manufacturers is considered different (see response A5.i) |
| ii. Please clarify why a once-daily oil-in water dose of 0.1% was the preferred formulation for Ikervis in the SANSIKA and SICCANOVE trials. | The dosing regimen of Ikervis is based on the results of PK studies conducted in rabbits that received single or repeated administrations of NOVA22007, which were compared to once or twice daily instillations of Restasis, an eye drop emulsion containing 0.05% ciclosporin:<br>• In a single dose PK study (Study N09F1205), the maximal concentration (Cmax) in the cornea produced by NOVA22007 0.1% was approximately 4-fold the Cmax produced by Restasis (2,692 vs. 748 ng/g) and the drug exposure in cornea (AUC) produced by NOVA22007 0.1% was about 3.6-fold the AUC produced by Restasis (51,373 vs. 14,210 ng.hr/g).<br>• A second PK study (Study N09F0306) demonstrated that similar tissue CsA concentrations (Cmin) were observed in the cornea at steady state following repeated administrations (for 10 days) of NOVA22007 0.1% QD as those observed following a 10-day treatment with Restasis (0.05%) BID (905.24±341.68 vs. 659.51±156.49 ng/g, respectively). No accumulation was found in the conjunctiva with |

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| | | NOVA22007 0.1% QD or with Restasis BID due to the high clearance of CsA from this tissue.<br><br>With these studies it was concluded that NOVA22007 0.1% QD appeared to be similar to Restasis BID in terms of target tissue (cornea and conjunctiva) exposure in rabbits. From the safety standpoint, the 0.1% dose was shown to be safe and well tolerated in a 28–day ocular safety and tolerance study conducted in rabbits (with administrations as frequent as 4 times daily for up to one month). Moreover, there was no significant systemic exposure to CsA at the dose level 0.1% in non-clinical studies (Study N09F1205, Study N09F0306 and Study Tp118). Of note, the US approved dose of Restasis 0.05% (0.5mg/mL) is one drop BID.<br><br>The choice of the dose was endorsed by CHMP during a scientific advice in 2006. |
| iii. | Please clarify whether, in terms of its consistency, the Ikervis eye drop is similar to Restasis rather than Optimmune, i.e. is more liquid based than ointment/gel based. | Ikervis and Restasis are emulsions and Optimmune is an ointment. Both emulsions have a similar consistency. Ikervis has the same consistency as milk. |
| iv. | Please clarify why cetalkonium chloride (CKC) was preferred to benzalkonium chloride (BAK) as the excipient for Ikervis in SANSIKA. | During initial development benzalkonium chloride (BAK) was selected because of its extensive use in approved ophthalmic formulations. This formulation was used in the initial pharmaceutical, nonclinical and clinical development. Subsequently, BAK was replaced by CKC since this is the most lipophilic of the three homologues in BAK. The selection of CKC instead of BAK resulted in a reduction of the amount of quaternary ammonium used by a factor of 4. |
| v. | Please clarify whether, as a consequence of using different excipients in the two trials, the Ikervis formulation in each trial should be considered to be similar or not. | Ikervis formulations in each trial are considered similar. This was further confirmed by the CHMP during a scientific advice in December 2010. |
| A5. | **Priority question: Relevant trials in the company's submission:** Table B2 | |

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| | of the company's submission lists 31 relevant RCTs, six of which included ciclosporin (and five of these six included a comparison of ciclosporin to vehicle). | |
| i. | Please clarify whether the company considers the comparator treatments in all studies in which a comparator arm is a vehicle to be of equal efficacy or whether vehicles may be considered to differ across studies. | We consider that vehicles used in different studies may differ in their efficacy and tolerability depending on the excipients used in the formulation. |
| ii. | Only SANSIKA and SICCANOVE are considered to be "pivotal" or "supportive" and are used to derive evidence that is presented in the company's submission. Please provide a rationale for the exclusion of the other four trials which studied ciclosporin (Kim 2009, ORA 2009, Sall 2000 and Stevenson 2000). | The publications Kim 2009, Sall 2000 and Stevenson 2000 compared other ciclosporins (Restasis) and not Ikervis. ORA 2009 used Ikervis but not in the severe population; the patients included in ORA had a mild to moderate DED and thus the study was not considered to be pivotal or supportive to the research question. |
| iii. | Figure B1 shows that 29 studies have been excluded because of "outcomes". Guidance recommends that studies are not excluded for this reason because of selective reporting (the outcome may have been measured but not reported). Please clarify if there were other reasons to support the exclusion of these studies. | Studies were excluded if outcomes specified in the systematic review protocol were not reported as defined in the protocol. |
| A6. | Please clarify whether data were collected on whether patients had aqueous-deficient or evaporative dry eye disease (DED) in the SANSIKA and SICCANOVE trials? If so, please present the proportion of patients with each type of DED by treatment arm for both trials individually. | The subtype of DED (aqueous-deficient or evaporative) was not captured in SANSIKA and SICCANOVE studies. |
| A7. | Table B6 of the company's submission states a secondary outcome for SANSIKA was "CFS improvement ≥2 points and global ocular discomfort improvement (VAS) ≥30%". However, this outcome does not appear to be reported in the company's submission or clinical study report. Please could you | The results are available in the SANSIKA CSR table 21. |

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| | clarify this discrepancy? | |
| A8. | Page 86 of the company's submission states that in SICCANOVE, "the rate of CFS-OSDI responders in the targeted population (patients with CFS grade 4 and OSDI ≥30%) was 5.6% with the vehicle and 30.8% with NOVA22007 (one drop per day), after 6 months of treatment." However, according to Table B6, CFS-OSDI response was not reported to be a primary or secondary outcome in SICCANOVE. Please could you clarify this discrepancy? | The rate of CFS-OSDI response was a post hoc analysis in the SICCANOVE study and was therefore not listed in table B6. |
| **Meta-analysis:** | | |
| A9. | Page 139 of the company's submission describes a "pre-specified meta-analysis of the SICCANOVE and SANSIKA studies" but on page 102, results are presented only for patients with Sjögren syndrome (SS). Please provide more information on this pre-specified meta-analysis, in particular: | |
| i. | When was this analysis pre-specified? | In 2012, before getting the results of the Phase III SANSIKA pivotal study and before breaking the codes, agreement on meta-analyses of the two Phase III studies (SANSIKA and SICCANOVE) and on the safety clinical package, including the potential RMP, was sought from national agencies (AEMPS in Spain, MPA in Sweden, and MHRA in the UK). Therefore, the results of the SICCANOVE study were available but the SANSIKA study was still masked. |
| ii. | Was a fixed or random effects model used? | A fixed effects model has been used. |
| iii. | Please provide the results from this meta-analysis. | A full report of the meta-analysis is provided. |
| iv. | Please provide similar meta-analyses (in a table and forest plot similar to Table B14 and Figure B4 of the company's submission) for ALL FAS and Severe | See below |

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| | |
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| FAS patients without SS. | |

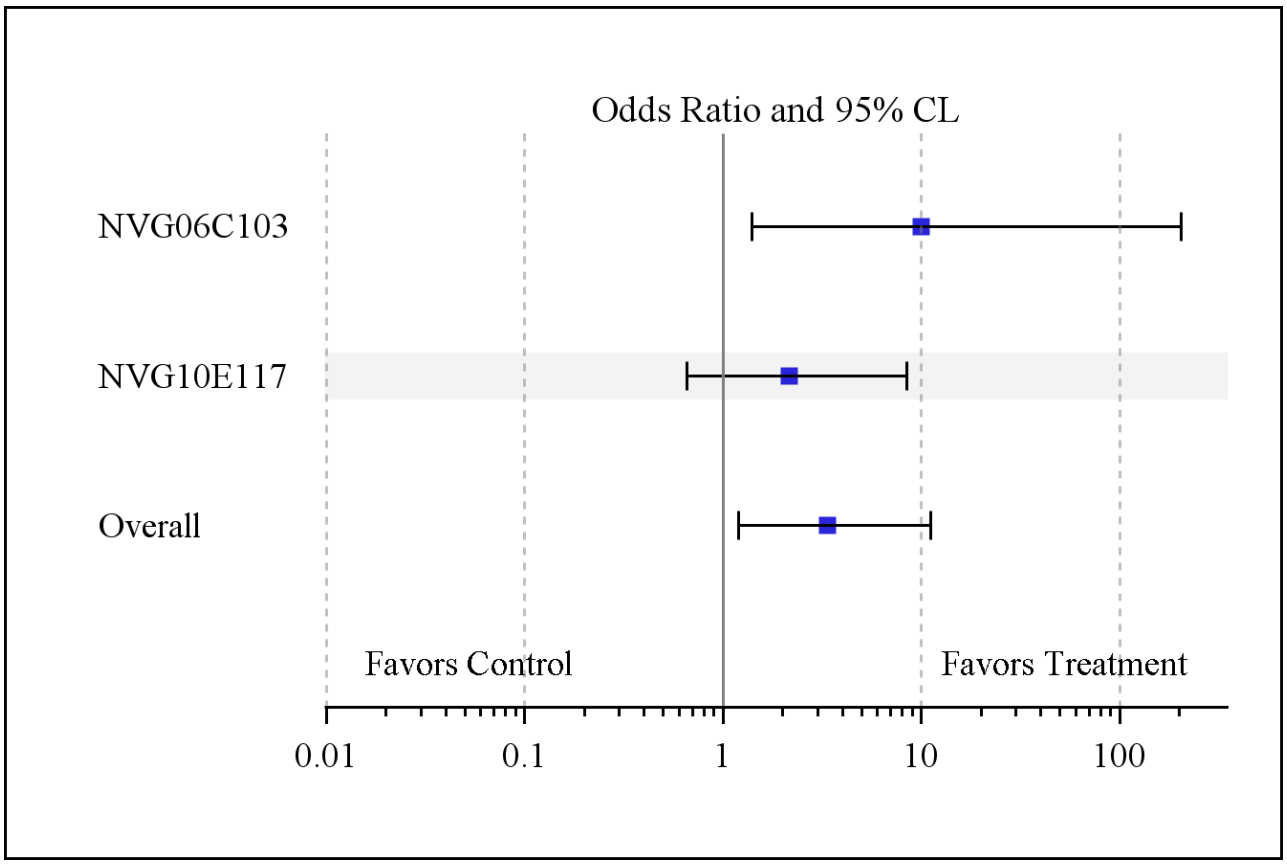


**Figure A9.iv.1 CFS/OSDI response at Month 6 (imputed data) in the patients with Sjögren in SEVERE FAS**

**Table A9.vi.1 CFS/OSDI response at Month 6 (imputed data) in the patients without Sjögren set in ALL FAS**

| | | IKERVIS (n=248) | | Vehicle (n=217) | |
|---|---|---|---|---|---|
| SANSIKA | | **n** | **%** | **n** | **%** |
| | Responders | 32 | 33.3 | 17 | 29.8 |
| | Non-responders | 64 | 66.7 | 40 | 70.2 |
| | Total | 96 | 100 | 57 | 100 |
| SICCANOVE | | **n** | **%** | **n** | **%** |
| | Responders | 25 | 16.6 | 13 | 8.5 |
| | Non-responders | 126 | 83.4 | 145 | 91.8 |
| | Total | 151 | 100 | 158 | 100 |
| SANSIKA + SICCANOVE | | **n** | **%** | **n** | **%** |
| | Responders | 57 | 23.1 | 30 | 14 |
| | Non-responders | 190 | 76.9 | 185 | 86 |
| | Total | 247 | 100 | 215 | 100 |

Logistic regression with Treatment Study Interaction

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p-value (Treatment)= 0.064

p-value (Study)= <0.001

p-value (Pooled country)= 0.330

p-value (Treatment Study interaction)= 0.223

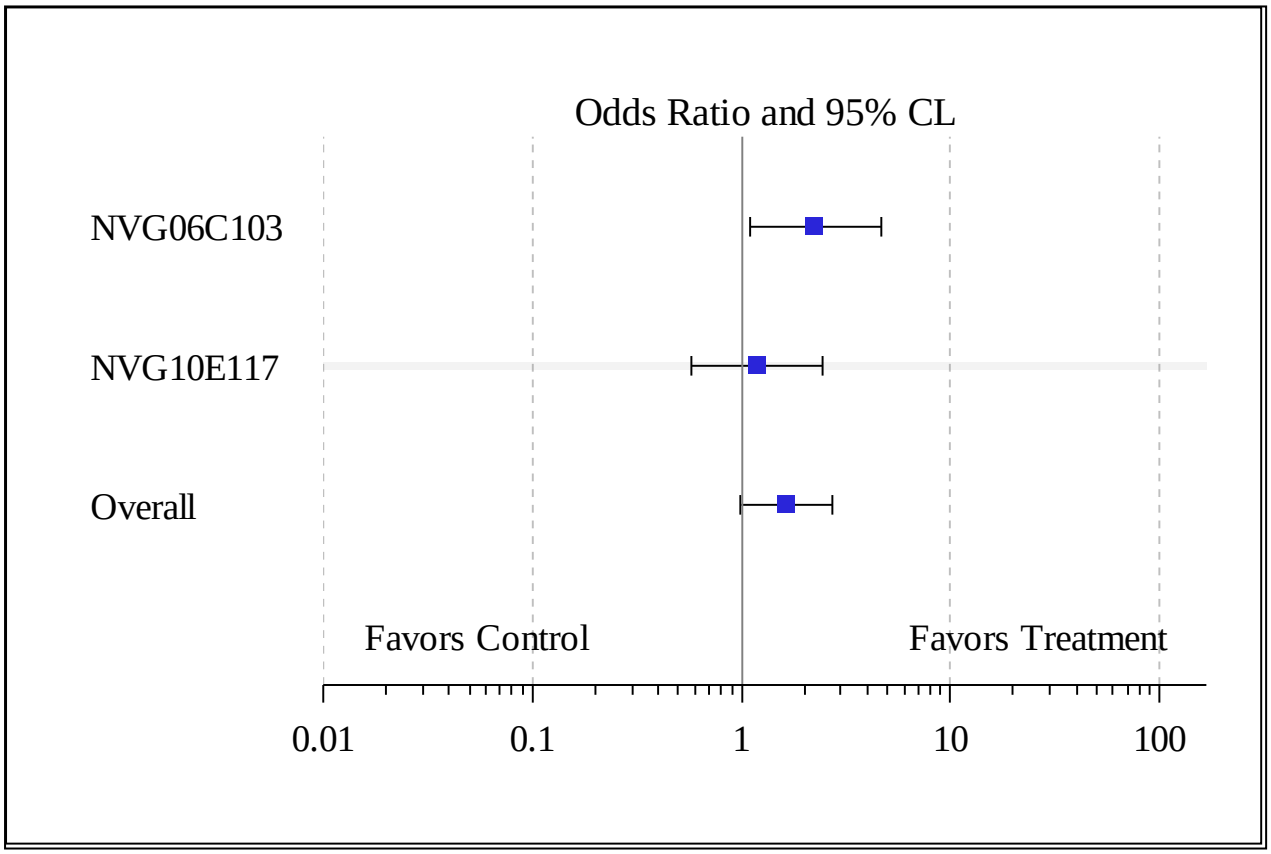


**Figure A9.iv.2 CFS/OSDI response at Month 6 (imputed data) in the patients without Sjögren set ALL FAS**

**Table A9.iv.2 CFS/OSDI response at Month 6 (imputed data) in the patients without Sjögren set in SEVERE PATIENTS**

| | | IKERVIS (n=116) | | Vehicle (n=73) | |
|---|---|---|---|---|---|
| SANSIKA | | **n** | **%** | **n** | **%** |
| | Responders | 32 | 33.3 | 17 | 29.8 |
| | Non-responders | 64 | 66.7 | 40 | 70.2 |
| | Total | 96 | 100 | 57 | 100 |
| SICCANOVE | | **n** | **%** | **n** | **%** |
| | Responders | 7 | 35.0 | 1 | 6.3 |
| | Non-responders | 13 | 65.0 | 15 | 93.8 |
| | Total | 20 | 100 | 16 | 100 |
| SANSIKA + SICCANOVE | | **n** | **%** | **n** | **%** |
| | Responders | 39 | 33.6 | 18 | 24.7 |

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| | | | | |
|---|---|---|---|---|
| Non-responders | 77 | 66.4 | 55 | 75.3 |
| Total | 116 | 100 | 73 | 100 |

Logistic regression with Treatment Study Interaction

p-value (Treatment)= 0.063

p-value (Study)= 0.177

p-value (Pooled country)= 0.069

p-value (Treatment Study interaction)= 0.119

| | | |
|---|---|---|
| v. | Please also provide similar meta-analyses (in a table and forest plot similar to Table B14 and Figure B4 of the company's submission) for ALL FAS and Severe FAS patients overall (i.e. with and without SS). | See below |

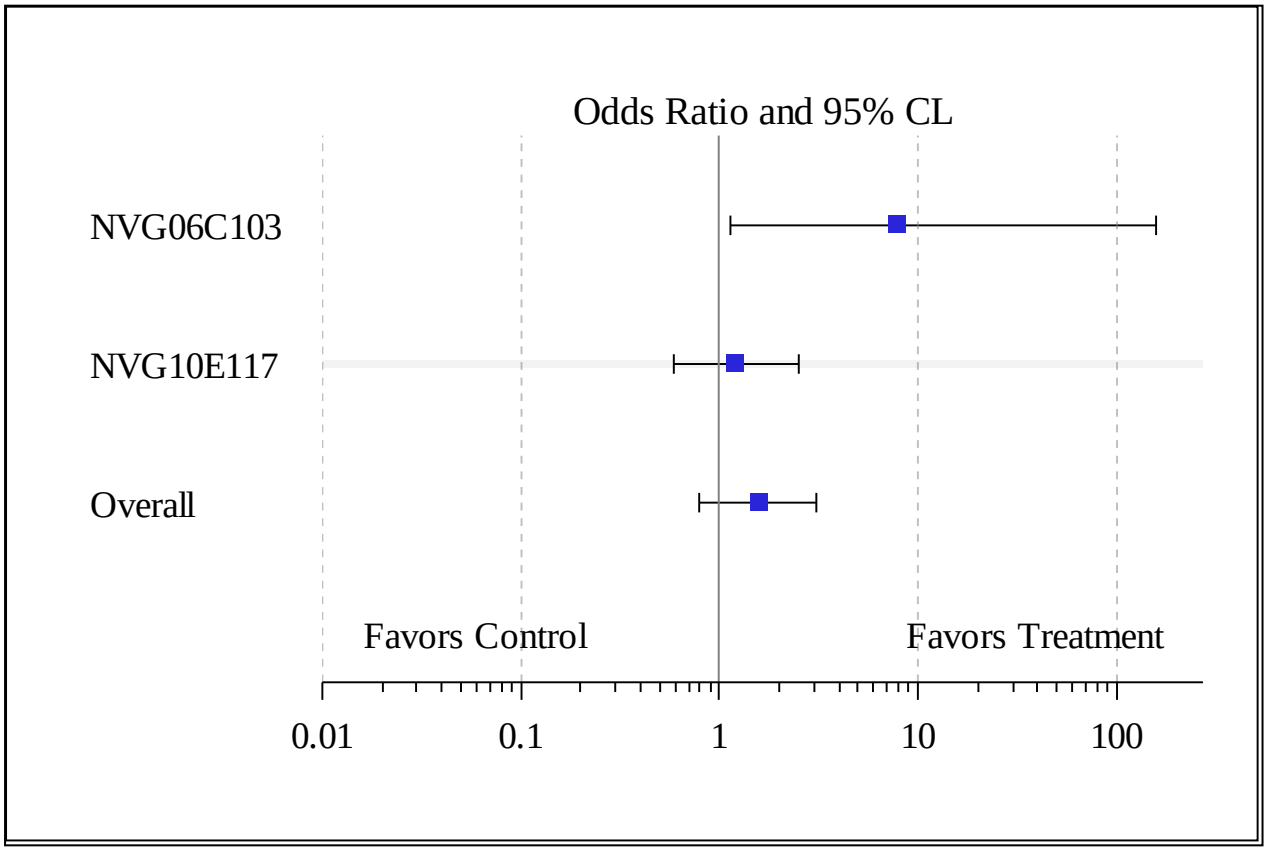


**Figure A9.v.1 CFS/OSDI response at Month 6 (imputed data) in the patients without Sjögren set SEVERE FAS**

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**Table A9.v.1 CFS/OSDI response at Month 6 (imputed data) in the ALL patients (with and without Sjögren) ALL FAS**

| | | IKERVIS (n=395) | | Vehicle (n=339) | |
|---|---|---|---|---|---|
| SANSIKA | | **n** | **%** | **n** | **%** |
| | Responders | 44 | 28.6 | 21 | 23.1 |
| | Non-responders | 110 | 71.4 | 70 | 76.9 |
| | Total | 154 | 100 | 91 | 100 |
| SICCANOVE | | **n** | **%** | **n** | **%** |
| | Responders | 41 | 17.2 | 23 | 9.4 |
| | Non-responders | 198 | 82.8 | 222 | 90.6 |
| | Total | 239 | 100 | 245 | 100 |
| SANSIKA + SICCANOVE | | **n** | **%** | **n** | **%** |
| | Responders | 85 | 21.6 | 44 | 13.1 |
| | Non-responders | 308 | 78.4 | 292 | 86.9 |
| | Total | 393 | 100 | 336 | 100 |

Logistic regression with Treatment Study Interaction

p-value (Treatment)= 0.020

p-value (Study)= <0.001

p-value (Pooled country)= 0.533

p-value (Treatment Study interaction)= 0.333

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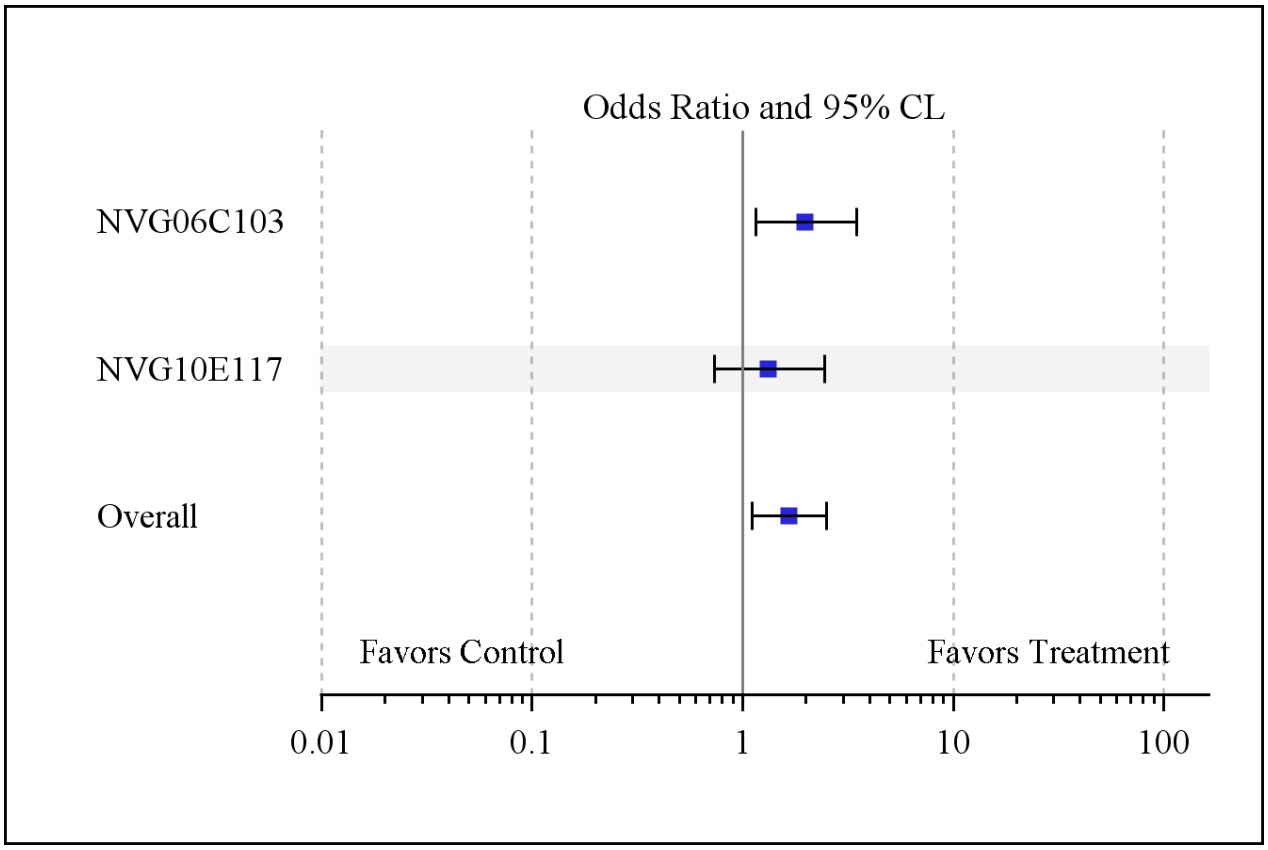


**Figure A9.v.2 CFS/OSDI response at Month 6 (imputed data) in the ALL patients set ALL FAS**

**Table A9.v.2 CFS/OSDI response at Month 6 (imputed data) in the ALL patients (with and without Sjögren) set in SEVERE PATIENTS**

| | | IKERVIS (n=193) | | Vehicle (n=126) | |
|---|---|---|---|---|---|
| SANSIKA | | **n** | **%** | **n** | **%** |
| | Responders | 44 | 28.6 | 21 | 23.1 |
| | Non-responders | 110 | 71.4 | 70 | 76.9 |
| | Total | 154 | 100 | 91 | 100 |
| SICCANOVE | | **n** | **%** | **n** | **%** |
| | Responders | 13 | 33.3 | 2 | 5.7 |
| | Non-responders | 26 | 66.7 | 33 | 94.3 |
| | Total | 39 | 100 | 35 | 100 |
| SANSIKA + SICCANOVE | | **n** | **%** | **n** | **%** |
| | Responders | 57 | 29.5 | 23 | 18.3 |
| | Non-responders | 136 | 70.5 | 103 | 81.7 |
| | Total | 193 | 100 | 126 | 100 |

Logistic regression with Treatment Study Interaction

p-value (Treatment)= 0.007

p-value (Study)= 0.150

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p-value (Pooled country)= 0.188

p-value (Treatment Study interaction)= 0.041

| | | |
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| A10. | There appear to be discrepancies in the presentation and/or interpretation of the evidence presented by the meta-analysis: | |
| i. | In Table B14, the data in the vehicle arm for SICCANOVE are identical to that for SANSIKA. Please clarify if this is correct or amend accordingly. | This is not correct.<br>The SANSIKA study should be: |

SANSIKA

| | IKERVIS (n=147~~395~~) | | Vehicle (n=~~339~~122) | |
|---|---|---|---|---|
| | n | % | n | % |
| Responders | 12 | 20.7 | ~~410~~ | 11.~~85~~ |
| Non-responders | 46 | 79.3 | 30~~77~~ | 88.~~25~~ |
| Total | 58 | 100 | 34~~87~~ | 100 |

| | | |
|---|---|---|
| ii. | Page 103 of the company's submission states: "There was no difference observed when analysing the Sjögren severe set in the severe FAS data as detailed in Table B15 below." However, the p-value in Table B15 is presented as 0.028 implying that there was a statistically significant difference. Please could you clarify this discrepancy? | This sentence relates to the Sjögren set in the all FAS dataset (p=0.113). However in the Sjögren set in the severe FAS dataset, the difference between the groups reached the statistical significance (p=0.028). |
| iii. | Please provide a forest plot for the findings reported in Table B15 (similar to Figure B4). | Provided below |

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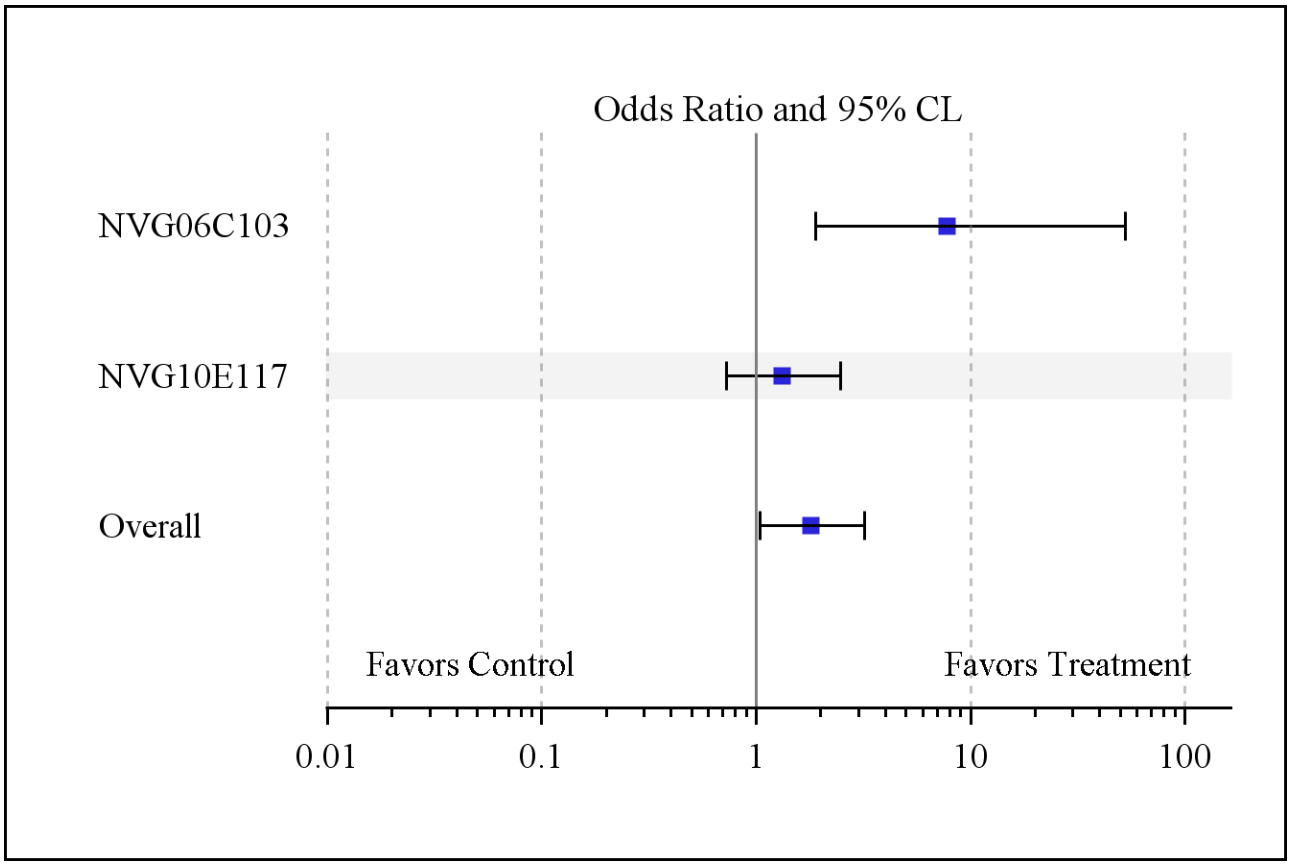


**Figure A10.iii.1 CFS/OSDI response at Month 6 (imputed data) in the ALL patients set SEVERE FAS**

| | | |
|---|---|---|
| **Safety data:** | | |
| A11. | Page 133 of the company's submission states that safety data were pooled. Please could you clarify whether you conducted a meta-analysis when pooling the safety data? | Data from the two phase III studies (pivotal SANSIKA study and supportive SICCANOVE study) were pooled to assess the safety. No specific meta-analysis model was used for the analysis, descriptive statistics were provided. |
| A12. | There appears to be discrepancies in the presentation of the safety data in Table B21. For example, the frequency of meibomianitis and lacrimal disorder in SICCANOVE (reported on page 135) exceed the number of pooled events for meibomianitis and lacrimal disorder reported in Table B21. Please could you clarify this? | In the text, the numbers refer to the number of events. The table refers to the number of patients experiencing an event. In SICCANOVE, 29 events occurred in 26 patients, 14 in the active treatment arm and 12 in the vehicle arm. Table should be amended to:<br>• **Intervention (n (%) of patients)**<br>• **Comparator (n (%) of patients)** |
| A13. | Serious adverse events (SAEs) are | The SAE was considered definitely related |

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|---|---|---|
| | reported on page 136 of the company's submission for both SANSIKA and SICCANOVE. Please clarify how many SAEs were in each treatment arm in each trial. Please also clarify if the SAE that was considered to be definitely related to the study drug in SICCANOVE was in the ciclosporin or vehicle arm. | to ciclosporin by the investigator. |
| A14. | Alongside SAEs, severe AEs are also described in the company's submission. | |
| i. | Please clarify the difference between a SAE and severe AE. | A serious adverse event (SAE) is defined as any AE meeting one of the following seriousness criteria:<br>- Results in death<br>- Is life-threatening (any adverse event that places the subject at immediate risk of death as it occurs)<br>- Requires inpatient hospitalization or prolongation of existing hospitalization<br>- Results in persistent or significant disability or incapacity<br>- Results in a congenital anomaly/birth effect<br>- Is medically important.<br>A severe AE is an event very distressing which interferes with normal daily life (e.g. patient spontaneously reports event without being prompted and states its impact on their daily life). |
| ii. | Severe ocular AEs are reported for SICCANOVE on page 135 of the company's submission and severe AEs reported for the second phase of SANSIKA on page 137 but similar data are not reported for the first phase of SANSIKA. Please clarify and report these data if available. | See SANSIKA CSR.<br>For part 1 of the SANSIKA study, severe ocular TEAEs, which were all treatment related, were reported in a higher proportion of patients treated with NOVA22007 (16 events in 9 patients, 5.8%) than with vehicle (8 events in 5 patients, 5.6%). For part 2, severe ocular TEAEs, which were all considered to be related to treatment, were reported in a similar proportion of patients in the NOVA22007/NOVA22007 group (2 events in 1 patient, 0.8%) and in the vehicle/NOVA22007 group (1 event in 1 patient, 1.3%). |
| iii. | Page 138 states "with the change from the BAK formulation to the | The numbers presented relate to the comparison of safety databases between |

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|---|---|---|
| | CKC formulation, ocular AEs decreased in severity from 27.5% to 6.2%." Please clarify what these proportions relate to (e.g. do they relate to an incidence of severe AEs and if so, in which population? Are they some type of measure of severity intensity?). | the BAK or CKC formulations. Data from the SICCANOVE phase III study and the Sjögren phase II study (BAK) were pooled and compared to data from SANSIKA phase III and ORA phase II (CKC). A smaller proportion of ocular severe events were observed in the CKC formulation than in the BAK formulation.<br>The severity was assessed during the studies as follows:<br>– Mild: event present but not distressing (e.g. patient reports the event only after being prompted)<br>– Moderate: event distressing, but does not interfere with normal daily life<br>– Severe: very distressing and interferes with the normal daily life. |
| A15. | Please could you provide further details on the difference between treatment emergent adverse events and treatment related adverse events (section 6.6 of the company's submission)? | A treatment emergent adverse event represents any event that occurs after the first instillation of the product, i.e. any event occurring after the baseline visit (related or not related to study medication). A treatment related adverse event represents an event considered by the investigator to be related to the study medication. |
| **Health-related quality of life data:** | | |
| A16. | Page 78 of the company's submission states that EQ-5D was used in SANSIKA to estimate health utility values. Please could you clarify which tariff you used when estimating the EQ-5D utility values? | The tariff used is based on UK data in 1993 (Rabin et al, 2011). |

**Section B: Clarification on cost-effectiveness data**

Questions B1-B5 have been asked in order to check the validation of key issues in the economic model.

| | | Response |
|---|---|---|
| B1. | **Priority question: Age/Sex Distribution.** Please provide a breakdown of patient numbers at baseline for all patients in the SANSIKA trial (Part 1) by Age in 5 year age bands and by Sex as follows: | Provided below |

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**Table B1.1 age/sex distribution for patients in SANSIKA trial (part 1) FAS population**

| | Males | Females |
|---|---|---|
| Age band (years) | N | N |
| 20-24 | 2 | 1 |
| 25-29 | 1 | 1 |
| 30-34 | - | 4 |
| 35-39 | 3 | 8 |
| 40-44 | 1 | 6 |
| 45-49 | 3 | 14 |
| 50-54 | 4 | 19 |
| 55-59 | 6 | 23 |
| 60-64 | 6 | 45 |
| 65-69 | 4 | 29 |
| 70-74 | 3 | 30 |
| 75-79 | 1 | 18 |
| 80-84 | 1 | 8 |
| 85-89 | 1 | 3 |
| Total | 36 | 209 |

| | | |
|---|---|---|
| B2. | **Priority question: Mean EQ-5D scores at Baseline by Age & Sex.** Please provide an analysis of baseline EQ-5D utility values in the SANSIKA trial, analysed by 5 year age-bands and sex as in the sample table below. EQ-5D utility values should be estimated using the UK valuation social tariff (Dolan et al 1997, CHE Discussion Paper 138), and relate only to patients completing all 5 dimensions of the questionnaire (i.e. no imputation of missing values). | Provided below |

**B2.1 Mean EQ-5D scores at Baseline by Age & Sex: SANSIKA FAS - Pooled Group**

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| Age band (years) | N | Mean | St devn | N | Mean | St devn |
| 20-24 | 2 | 0.845 | 0.220 | 1 | 1.000 | - |
| 25-29 | 1 | 0.760 | - | 1 | 0.689 | - |
| 30-34 | - | - | - | 4 | 0.889 | 0.129 |
| 35-39 | 2 | 0.459 | 0.376 | 8 | 0.681 | 0.281 |
| 40-44 | 1 | 1.000 | - | 6 | 0.880 | 0.137 |
| 45-49 | 3 | 0.852 | 0.129 | 14 | 0.714 | 0.250 |

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| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| Age band (years) | N | Mean | St devn | N | Mean | St devn |
| 50-54 | 4 | 0.669 | 0.303 | 18 | 0.659 | 0.377 |
| 55-59 | 6 | 0.757 | 0.057 | 23 | 0.641 | 0.243 |
| 60-64 | 6 | 0.765 | 0.277 | 44 | 0.617 | 0.289 |
| 65-69 | 4 | 0.843 | 0.116 | 29 | 0.648 | 0.324 |
| 70-74 | 3 | 0.336 | 0.355 | 30 | 0.684 | 0.227 |
| 75-79 | 1 | 0.689 | - | 13 | 0.587 | 0.256 |
| 80-84 | 1 | 0.587 | - | 7 | 0.396 | 0.355 |
| 85-89 | 1 | 1.000 | - | 3 | 0.324 | 0.361 |
| Total | 35 | 0.725 | 0.250 | 201 | 0.649 | 0.289 |

**Table B2.2 Mean EQ-5D scores at Baseline by Age & Sex: SANSIKA FAS - NOVA22007 Group**

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| Age band (years) | N | Mean | St devn | N | Mean | St devn |
| 20-24 | 2 | 0.845 | 0.220 | 1 | 1.000 | - |
| 25-29 | 1 | 0.760 | - | 1 | 0.689 | - |
| 30-34 | - | - | - | 3 | 0.932 | 0.118 |
| 35-39 | 1 | 0.725 | - | 2 | 0.708 | 0.024 |
| 40-44 | 1 | 1.000 | - | 6 | 0.880 | 0.137 |
| 45-49 | 3 | 0.852 | 0.129 | 8 | 0.764 | 0.285 |
| 50-54 | 3 | 0.696 | 0.365 | 9 | 0.674 | 0.429 |
| 55-59 | 4 | 0.756 | 0.068 | 15 | 0.651 | 0.253 |
| 60-64 | 4 | 0.834 | 0.129 | 29 | 0.621 | 0.288 |
| 65-69 | 2 | 0.898 | 0.144 | 17 | 0.653 | 0.341 |
| 70-74 | 3 | 0.336 | 0.355 | 18 | 0.629 | 0.246 |
| 75-79 | 1 | 0.689 | - | 6 | 0.435 | 0.306 |
| 80-84 | 1 | 0.587 | - | 5 | 0.363 | 0.365 |
| 85-89 | 1 | 1.000 | - | 2 | 0.123 | 0.140 |
| Total | 27 | 0.750 | 0.239 | 122 | 0.641 | 0.306 |

**Table B2.3 Mean EQ-5D scores at Baseline by Age & Sex: SANSIKA FAS - Vehicle Group**

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| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| Age band (years) | N | Mean | St devn | N | Mean | St devn |
| 30-34 | - | - | - | 1 | 0.760 | - |
| 35-39 | 1 | 0.193 | - | 6 | 0.672 | 0.332 |
| 45-49 | - | - | - | 6 | 0.649 | 0.199 |
| 50-54 | 1 | 0.587 | - | 9 | 0.644 | 0.343 |
| 55-59 | 2 | 0.761 | 0.050 | 8 | 0.624 | 0.240 |
| 60-64 | 2 | 0.628 | 0.527 | 15 | 0.610 | 0.300 |
| 65-69 | 2 | 0.789 | 0.087 | 12 | 0.640 | 0.314 |
| 70-74 | - | - | - | 12 | 0.768 | 0.171 |
| 75-79 | - | - | - | 7 | 0.718 | 0.100 |
| 80-84 | - | - | - | 2 | 0.478 | 0.450 |
| 85-89 | - | - | - | 1 | 0.725 | - |
| Total | 8 | 0.642 | 0.284 | 79 | 0.661 | 0.261 |

| | | |
|---|---|---|
| B3. | **Priority question: Mean EQ-5D results by Response.** Please provide a revised and extended version of Table B33 in the company's submission (as per Table B1 and Table B2 below). Only patients with valid EQ-5D responses to all 5 dimensions at baseline and at 6 months should be included. EQ-5D utility values should be estimated using the UK valuation social tariff (Dolan et al 1997, CHE Discussion Paper 138), and utility increments (6 months – baseline) should be calculated pairwise for each patient. | Provided below |

**Table B3.1 Definition of response in SANSIKA (primary endpoint) - Pooled Group**

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| | Responders | Non-responders |
|---|---|---|
| Patient numbers | 59 | 137 |
| Mean EQ-5D utility score at baseline | 0.654 | 0.669 |
| Mean EQ-5D utility score at 6 months | 0.723 | 0.666 |
| Mean EQ-5D utility change (6 months–baseline) | 0.069 | -0.003 |
| Standard deviation of estimated utility change | 0.198 | 0.251 |
| Standard error of estimated utility change | 0.026 | 0.021 |
| Attributable difference in utility change: Mean | 0.072 | - |
| Standard deviation | 0.237 | - |
| Standard error | 0.037 | - |

**Table B3.2 Definition of response in SANSIKA (primary endpoint) - NOVA22007 Group**

| | Responders | Non-responders |
|---|---|---|
| Patient numbers | 39 | 82 |
| Mean EQ-5D utility score at baseline | 0.636 | 0.665 |
| Mean EQ-5D utility score at 6 months | 0.692 | 0.666 |
| Mean EQ-5D utility change (6 months–baseline) | 0.056 | 0.001 |
| Standard deviation of estimated utility change | 0.228 | 0.264 |
| Standard error of estimated utility change | 0.036 | 0.029 |
| Attributable difference in utility change: Mean | 0.055 | - |
| Standard deviation | 0.253 | - |
| Standard error | 0.049 | - |

**Table B3.3 Definition of response in SANSIKA (primary endpoint) - Vehicle Group**

| | Responders | Non-responders |
|---|---|---|
| Patient numbers | 20 | 55 |
| Mean EQ-5D utility score at baseline | 0.688 | 0.676 |
| Mean EQ-5D utility score at 6 months | 0.783 | 0.667 |
| Mean EQ-5D utility change (6 months–baseline) | 0.095 | -0.009 |
| Standard deviation of estimated utility change | 0.123 | 0.233 |
| Standard error of estimated utility change | 0.027 | 0.031 |
| Attributable difference in utility change: Mean | 0.104 | - |
| Standard deviation | 0.210 | - |
| Standard error | 0.055 | - |

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**Table B3.4 Post-hoc definition of response in SANSIKA - Pooled Group**

| | Responders | Non-responders |
|---|---|---|
| Patient numbers | 33 | 163 |
| Mean EQ-5D utility score at baseline | 0.624 | 0.673 |
| Mean EQ-5D utility score at 6 months | 0.729 | 0.674 |
| Mean EQ-5D utility change (6 months–baseline) | 0.105 | 0.001 |
| Standard deviation of estimated utility change | 0.221 | 0.239 |
| Standard error of estimated utility change | 0.038 | 0.019 |
| Attributable difference in utility change: Mean | 0.104 | - |
| Standard deviation | 0.236 | - |
| Standard error | 0.045 | - |

**Table B3.5 Post-hoc definition of response in SANSIKA - NOVA22007 Group**

| | Responders | Non-responders |
|---|---|---|
| Patient numbers | 26 | 95 |
| Mean EQ-5D utility score at baseline | 0.607 | 0.669 |
| Mean EQ-5D utility score at 6 months | 0.703 | 0.667 |
| Mean EQ-5D utility change (6 months–baseline) | 0.095 | -0.002 |
| Standard deviation of estimated utility change | 0.241 | 0.254 |
| Standard error of estimated utility change | 0.047 | 0.026 |
| Attributable difference in utility change: Mean | 0.097 | - |
| Standard deviation | 0.251 | - |
| Standard error | 0.056 | - |

**Table B3.6 Post-hoc definition of response in SANSIKA - Vehicle Group**

| | Responders | Non-responders |
|---|---|---|
| Patient numbers | 7 | 68 |
| Mean EQ-5D utility score at baseline | 0.684 | 0.678 |
| Mean EQ-5D utility score at 6 months | 0.825 | 0.685 |
| Mean EQ-5D utility change (6 months–baseline) | 0.141 | 0.006 |
| Standard deviation of estimated utility change | 0.128 | 0.218 |
| Standard error of estimated utility change | 0.048 | 0.026 |
| Attributable difference in utility change: Mean | 0.135 | - |
| Standard deviation | 0.212 | - |
| Standard error | 0.084 | - |

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|---|---|
| B4. **Priority question: Treatment Discontinuation**. Please provide results of Kaplan-Meier analyses of the FAS data set from the SANSIKA clinical trial for Time to Treatment Discontinuation as follows: | |
| i. For patients in the Ikervis arm, including time on allocated treatment from baseline to the end of Part 2 of the trial. | Provided below |

**Table B4.i.1** Kaplan-Meier Analysis on Treatment Discontinuation: SANSIKA FAS - Ikervis arm

| Product-Limit Survival Estimates | | | | | | |
|---|---|---|---|---|---|---|
| exdy | | Survival | Failure | Survival Standard Error | Number Failed | Number Left |
| 0.000 | | 1.0000 | 0 | 0 | 0 | 154 |
| 4.000 | | 0.9935 | 0.00649 | 0.00647 | 1 | 153 |
| 7.000 | | 0.9870 | 0.0130 | 0.00912 | 2 | 152 |
| 13.000 | | 0.9805 | 0.0195 | 0.0111 | 3 | 151 |
| 15.000 | | 0.9740 | 0.0260 | 0.0128 | 4 | 150 |
| 18.000 | | 0.9675 | 0.0325 | 0.0143 | 5 | 149 |
| 28.000 | | - | - | - | 6 | 148 |
| 28.000 | | - | - | - | 7 | 147 |
| 28.000 | | - | - | - | 8 | 146 |
| 28.000 | | 0.9416 | 0.0584 | 0.0189 | 9 | 145 |
| 39.000 | | 0.9351 | 0.0649 | 0.0199 | 10 | 144 |
| 62.000 | | 0.9286 | 0.0714 | 0.0208 | 11 | 143 |
| 69.000 | | - | - | - | 12 | 142 |
| 69.000 | | 0.9156 | 0.0844 | 0.0224 | 13 | 141 |
| 78.000 | | 0.9091 | 0.0909 | 0.0232 | 14 | 140 |
| 79.000 | * | - | - | - | 14 | 139 |
| 84.000 | | 0.9026 | 0.0974 | 0.0239 | 15 | 138 |
| 91.000 | * | - | - | - | 15 | 137 |
| 98.000 | | - | - | - | 16 | 136 |
| 98.000 | | 0.8894 | 0.1106 | 0.0253 | 17 | 135 |
| 101.000 | | 0.8828 | 0.1172 | 0.0260 | 18 | 134 |

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| Product-Limit Survival Estimates | | | | | | |
|---|---|---|---|---|---|---|
| exdy | | Survival | Failure | Survival Standard Error | Number Failed | Number Left |
| 115.000 | | 0.8762 | 0.1238 | 0.0266 | 19 | 133 |
| 172.000 | * | - | - | - | 19 | 132 |
| 181.000 | | 0.8696 | 0.1304 | 0.0272 | 20 | 131 |
| 189.000 | | - | - | - | 21 | 130 |
| 189.000 | | 0.8563 | 0.1437 | 0.0284 | 22 | 129 |
| 194.000 | | 0.8496 | 0.1504 | 0.0289 | 23 | 128 |
| 214.000 | | 0.8430 | 0.1570 | 0.0294 | 24 | 127 |
| 215.000 | | 0.8364 | 0.1636 | 0.0299 | 25 | 126 |
| 231.000 | | 0.8297 | 0.1703 | 0.0304 | 26 | 125 |
| 249.000 | | 0.8231 | 0.1769 | 0.0309 | 27 | 124 |
| 252.000 | | - | - | - | 28 | 123 |
| 252.000 | | 0.8098 | 0.1902 | 0.0318 | 29 | 122 |
| 253.000 | | 0.8032 | 0.1968 | 0.0322 | 30 | 121 |
| 269.000 | | 0.7965 | 0.2035 | 0.0326 | 31 | 120 |
| 303.000 | | 0.7899 | 0.2101 | 0.0330 | 32 | 119 |
| 308.000 | | 0.7833 | 0.2167 | 0.0334 | 33 | 118 |
| 319.000 | * | - | - | - | 33 | 117 |
| 323.000 | * | - | - | - | 33 | 116 |
| 327.000 | * | - | - | - | 33 | 115 |
| 328.000 | * | - | - | - | 33 | 114 |
| 328.000 | * | - | - | - | 33 | 113 |
| 329.000 | * | - | - | - | 33 | 112 |
| 329.000 | * | - | - | - | 33 | 111 |
| 329.000 | * | - | - | - | 33 | 110 |
| 330.000 | * | - | - | - | 33 | 109 |
| 332.000 | * | - | - | - | 33 | 108 |
| 333.000 | * | - | - | - | 33 | 107 |
| 334.000 | * | - | - | - | 33 | 106 |
| 335.000 | * | - | - | - | 33 | 105 |
| 336.000 | | 0.7758 | 0.2242 | 0.0339 | 34 | 104 |

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| Product-Limit Survival Estimates | | | | | | |
|---|---|---|---|---|---|---|
| exdy | | Survival | Failure | Survival Standard Error | Number Failed | Number Left |
| 336.000 | * | - | - | - | 34 | 103 |
| 336.000 | * | - | - | - | 34 | 102 |
| 336.000 | * | - | - | - | 34 | 101 |
| 339.000 | * | - | - | - | 34 | 100 |
| 340.000 | * | - | - | - | 34 | 99 |
| 340.000 | * | - | - | - | 34 | 98 |
| 341.000 | * | - | - | - | 34 | 97 |
| 341.000 | * | - | - | - | 34 | 96 |
| 342.000 | * | - | - | - | 34 | 95 |
| 343.000 | * | - | - | - | 34 | 94 |
| 343.000 | * | - | - | - | 34 | 93 |
| 343.000 | * | - | - | - | 34 | 92 |
| 343.000 | * | - | - | - | 34 | 91 |
| 343.000 | * | - | - | - | 34 | 90 |
| 343.000 | * | - | - | - | 34 | 89 |
| 343.000 | * | - | - | - | 34 | 88 |
| 344.000 | * | - | - | - | 34 | 87 |
| 344.000 | * | - | - | - | 34 | 86 |
| 345.000 | * | - | - | - | 34 | 85 |
| 345.000 | * | - | - | - | 34 | 84 |
| 348.000 | * | - | - | - | 34 | 83 |
| 348.000 | * | - | - | - | 34 | 82 |
| 348.000 | * | - | - | - | 34 | 81 |
| 348.000 | * | - | - | - | 34 | 80 |
| 349.000 | * | - | - | - | 34 | 79 |
| 350.000 | * | - | - | - | 34 | 78 |
| 350.000 | * | - | - | - | 34 | 77 |
| 350.000 | * | - | - | - | 34 | 76 |
| 350.000 | * | - | - | - | 34 | 75 |
| 350.000 | * | - | - | - | 34 | 74 |

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| Product-Limit Survival Estimates | | | | | | |
|---|---|---|---|---|---|---|
| exdy | | Survival | Failure | Survival Standard Error | Number Failed | Number Left |
| 350.000 | * | - | - | - | 34 | 73 |
| 350.000 | * | - | - | - | 34 | 72 |
| 350.000 | * | - | - | - | 34 | 71 |
| 350.000 | * | - | - | - | 34 | 70 |
| 350.000 | * | - | - | - | 34 | 69 |
| 350.000 | * | - | - | - | 34 | 68 |
| 351.000 | * | - | - | - | 34 | 67 |
| 355.000 | * | - | - | - | 34 | 66 |
| 357.000 | | 0.7641 | 0.2359 | 0.0354 | 35 | 65 |
| 357.000 | * | - | - | - | 35 | 64 |
| 357.000 | * | - | - | - | 35 | 63 |
| 357.000 | * | - | - | - | 35 | 62 |
| 358.000 | * | - | - | - | 35 | 61 |
| 359.000 | * | - | - | - | 35 | 60 |
| 360.000 | * | - | - | - | 35 | 59 |
| 360.000 | * | - | - | - | 35 | 58 |
| 361.000 | | 0.7509 | 0.2491 | 0.0371 | 36 | 57 |
| 362.000 | * | - | - | - | 36 | 56 |
| 363.000 | * | - | - | - | 36 | 55 |
| 363.000 | * | - | - | - | 36 | 54 |
| 363.000 | * | - | - | - | 36 | 53 |
| 364.000 | * | - | - | - | 36 | 52 |
| 364.000 | * | - | - | - | 36 | 51 |
| 364.000 | * | - | - | - | 36 | 50 |
| 364.000 | * | - | - | - | 36 | 49 |
| 365.000 | * | - | - | - | 36 | 48 |
| 367.000 | * | - | - | - | 36 | 47 |
| 369.000 | * | - | - | - | 36 | 46 |
| 370.000 | * | - | - | - | 36 | 45 |
| 370.000 | * | - | - | - | 36 | 44 |

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| Product-Limit Survival Estimates | | | | | | |
|---|---|---|---|---|---|---|
| exdy | | Survival | Failure | Survival Standard Error | Number Failed | Number Left |
| 370.000 | * | - | - | - | 36 | 43 |
| 370.000 | * | - | - | - | 36 | 42 |
| 371.000 | * | - | - | - | 36 | 41 |
| 371.000 | * | - | - | - | 36 | 40 |
| 371.000 | * | - | - | - | 36 | 39 |
| 371.000 | * | - | - | - | 36 | 38 |
| 373.000 | * | - | - | - | 36 | 37 |
| 374.000 | * | - | - | - | 36 | 36 |
| 374.000 | * | - | - | - | 36 | 35 |
| 375.000 | * | - | - | - | 36 | 34 |
| 376.000 | * | - | - | - | 36 | 33 |
| 376.000 | * | - | - | - | 36 | 32 |
| 377.000 | * | - | - | - | 36 | 31 |
| 377.000 | * | - | - | - | 36 | 30 |
| 377.000 | * | - | - | - | 36 | 29 |
| 378.000 | * | - | - | - | 36 | 28 |
| 378.000 | * | - | - | - | 36 | 27 |
| 378.000 | * | - | - | - | 36 | 26 |
| 378.000 | * | - | - | - | 36 | 25 |
| 378.000 | * | - | - | - | 36 | 24 |
| 379.000 | | 0.7196 | 0.2804 | 0.0470 | 37 | 23 |
| 379.000 | * | - | - | - | 37 | 22 |
| 379.000 | * | - | - | - | 37 | 21 |
| 379.000 | * | - | - | - | 37 | 20 |
| 379.000 | * | - | - | - | 37 | 19 |
| 379.000 | * | - | - | - | 37 | 18 |
| 380.000 | * | - | - | - | 37 | 17 |
| 383.000 | * | - | - | - | 37 | 16 |
| 385.000 | * | - | - | - | 37 | 15 |
| 385.000 | * | - | - | - | 37 | 14 |

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| Product-Limit Survival Estimates | | | | | | |
|---|---|---|---|---|---|---|
| exdy | | Survival | Failure | Survival Standard Error | Number Failed | Number Left |
| 386.000 | * | - | - | - | 37 | 13 |
| 388.000 | * | - | - | - | 37 | 12 |
| 392.000 | * | - | - | - | 37 | 11 |
| 392.000 | * | - | - | - | 37 | 10 |
| 393.000 | * | - | - | - | 37 | 9 |
| 395.000 | * | - | - | - | 37 | 8 |
| 395.000 | * | - | - | - | 37 | 7 |
| 399.000 | * | - | - | - | 37 | 6 |
| 414.000 | * | - | - | - | 37 | 5 |
| 415.000 | * | - | - | - | 37 | 4 |
| 420.000 | * | - | - | - | 37 | 3 |
| 422.000 | * | - | - | - | 37 | 2 |
| 428.000 | * | - | - | - | 37 | 1 |
| 455.000 | * | - | - | - | 37 | 0 |

| | | |
|---|---|---|
| ii. | For patients in the Vehicle arm, including time on allocated treatment in Part 1 of the trial only. | Provided below |

**Table B4.ii.1 Kaplan-Meier Analysis on Treatment Discontinuation: SANSIKA FAS - Vehicle arm in Part1**

| Product-Limit Survival Estimates | | | | | | |
|---|---|---|---|---|---|---|
| exdy | | Survival | Failure | Survival Standard Error | Number Failed | Number Left |
| 0.000 | | 1.0000 | 0 | 0 | 0 | 89 |
| 33.000 | | 0.9888 | 0.0112 | 0.0112 | 1 | 88 |
| 40.000 | | 0.9775 | 0.0225 | 0.0157 | 2 | 87 |
| 90.000 | | 0.9663 | 0.0337 | 0.0191 | 3 | 86 |
| 91.000 | | 0.9551 | 0.0449 | 0.0220 | 4 | 85 |
| 106.000 | * | - | - | - | 4 | 84 |
| 134.000 | | 0.9437 | 0.0563 | 0.0245 | 5 | 83 |
| 135.000 | | 0.9323 | 0.0677 | 0.0267 | 6 | 82 |
| 145.000 | | 0.9209 | 0.0791 | 0.0287 | 7 | 81 |

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| Product-Limit Survival Estimates | | | | | | |
|---|---|---|---|---|---|---|
| exdy | | Survival | Failure | Survival Standard Error | Number Failed | Number Left |
| 154.000 | * | - | - | - | 7 | 80 |
| 154.000 | * | - | - | - | 7 | 79 |
| 154.000 | * | - | - | - | 7 | 78 |
| 155.000 | * | - | - | - | 7 | 77 |
| 161.000 | * | - | - | - | 7 | 76 |
| 161.000 | * | - | - | - | 7 | 75 |
| 161.000 | * | - | - | - | 7 | 74 |
| 161.000 | * | - | - | - | 7 | 73 |
| 161.000 | * | - | - | - | 7 | 72 |
| 162.000 | * | - | - | - | 7 | 71 |
| 163.000 | * | - | - | - | 7 | 70 |
| 163.000 | * | - | - | - | 7 | 69 |
| 164.000 | * | - | - | - | 7 | 68 |
| 166.000 | * | - | - | - | 7 | 67 |
| 167.000 | * | - | - | - | 7 | 66 |
| 167.000 | * | - | - | - | 7 | 65 |
| 167.000 | * | - | - | - | 7 | 64 |
| 168.000 | * | - | - | - | 7 | 63 |
| 168.000 | * | - | - | - | 7 | 62 |
| 168.000 | * | - | - | - | 7 | 61 |
| 170.000 | * | - | - | - | 7 | 60 |
| 172.000 | * | - | - | - | 7 | 59 |
| 172.000 | * | - | - | - | 7 | 58 |
| 173.000 | * | - | - | - | 7 | 57 |
| 173.000 | * | - | - | - | 7 | 56 |
| 173.000 | * | - | - | - | 7 | 55 |
| 174.000 | * | - | - | - | 7 | 54 |
| 174.000 | * | - | - | - | 7 | 53 |
| 174.000 | * | - | - | - | 7 | 52 |
| 174.000 | * | - | - | - | 7 | 51 |

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| Product-Limit Survival Estimates | | | | | | |
|---|---|---|---|---|---|---|
| exdy | | Survival | Failure | Survival Standard Error | Number Failed | Number Left |
| 174.000 | * | - | - | - | 7 | 50 |
| 174.000 | * | - | - | - | 7 | 49 |
| 175.000 | * | - | - | - | 7 | 48 |
| 175.000 | * | - | - | - | 7 | 47 |
| 175.000 | * | - | - | - | 7 | 46 |
| 175.000 | * | - | - | - | 7 | 45 |
| 175.000 | * | - | - | - | 7 | 44 |
| 175.000 | * | - | - | - | 7 | 43 |
| 175.000 | * | - | - | - | 7 | 42 |
| 176.000 | * | - | - | - | 7 | 41 |
| 176.000 | * | - | - | - | 7 | 40 |
| 176.000 | * | - | - | - | 7 | 39 |
| 176.000 | * | - | - | - | 7 | 38 |
| 177.000 | * | - | - | - | 7 | 37 |
| 177.000 | * | - | - | - | 7 | 36 |
| 177.000 | * | - | - | - | 7 | 35 |
| 178.000 | * | - | - | - | 7 | 34 |
| 179.000 | * | - | - | - | 7 | 33 |
| 180.000 | * | - | - | - | 7 | 32 |
| 181.000 | * | - | - | - | 7 | 31 |
| 181.000 | * | - | - | - | 7 | 30 |
| 182.000 | * | - | - | - | 7 | 29 |
| 182.000 | * | - | - | - | 7 | 28 |
| 182.000 | * | - | - | - | 7 | 27 |
| 182.000 | * | - | - | - | 7 | 26 |
| 182.000 | * | - | - | - | 7 | 25 |
| 182.000 | * | - | - | - | 7 | 24 |
| 182.000 | * | - | - | - | 7 | 23 |
| 182.000 | * | - | - | - | 7 | 22 |
| 182.000 | * | - | - | - | 7 | 21 |

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| Product-Limit Survival Estimates | | | | | | |
|---|---|---|---|---|---|---|
| exdy | | Survival | Failure | Survival Standard Error | Number Failed | Number Left |
| 182.000 | * | - | - | - | 7 | 20 |
| 183.000 | * | - | - | - | 7 | 19 |
| 183.000 | * | - | - | - | 7 | 18 |
| 186.000 | * | - | - | - | 7 | 17 |
| 188.000 | * | - | - | - | 7 | 16 |
| 189.000 | * | - | - | - | 7 | 15 |
| 189.000 | * | - | - | - | 7 | 14 |
| 190.000 | * | - | - | - | 7 | 13 |
| 190.000 | * | - | - | - | 7 | 12 |
| 191.000 | * | - | - | - | 7 | 11 |
| 193.000 | * | - | - | - | 7 | 10 |
| 193.000 | * | - | - | - | 7 | 9 |
| 193.000 | * | - | - | - | 7 | 8 |
| 196.000 | * | - | - | - | 7 | 7 |
| 196.000 | * | - | - | - | 7 | 6 |
| 196.000 | * | - | - | - | 7 | 5 |
| 196.000 | * | - | - | - | 7 | 4 |
| 197.000 | * | - | - | - | 7 | 3 |
| 223.000 | * | - | - | - | 7 | 2 |
| 230.000 | * | - | - | - | 7 | 1 |
| 241.000 | | 0 | 1.0000 | - | 8 | 0 |

| | | |
|---|---|---|
| iii. | For patients in the Vehicle arm, including time on Ikervis in Part 2 of the trial, beginning at the start of Part 2. | Provided below |

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**Table B4.iii.1 Kaplan-Meier Analysis on Treatment Discontinuation: SANSIKA FAS Vehicle arm in Part2 (Time on Ikervis)**

| Product-Limit Survival Estimates | | | | | | |
|---|---|---|---|---|---|---|
| exdy | | Survival | Failure | Survival Standard Error | Number Failed | Number Left |
| 0.000 | | 1.0000 | 0 | 0 | 0 | 79 |
| 7.000 | * | - | - | - | 0 | 78 |
| 28.000 | | 0.9872 | 0.0128 | 0.0127 | 1 | 77 |
| 29.000 | | 0.9744 | 0.0256 | 0.0179 | 2 | 76 |
| 33.000 | | 0.9615 | 0.0385 | 0.0218 | 3 | 75 |
| 61.000 | | 0.9487 | 0.0513 | 0.0250 | 4 | 74 |
| 68.000 | * | - | - | - | 4 | 73 |
| 70.000 | | 0.9357 | 0.0643 | 0.0278 | 5 | 72 |
| 77.000 | * | - | - | - | 5 | 71 |
| 101.000 | | 0.9225 | 0.0775 | 0.0304 | 6 | 70 |
| 101.000 | * | - | - | - | 6 | 69 |
| 121.000 | | 0.9092 | 0.0908 | 0.0328 | 7 | 68 |
| 131.000 | | 0.8958 | 0.1042 | 0.0349 | 8 | 67 |
| 140.000 | * | - | - | - | 8 | 66 |
| 150.000 | * | - | - | - | 8 | 65 |
| 151.000 | * | - | - | - | 8 | 64 |
| 153.000 | * | - | - | - | 8 | 63 |
| 154.000 | * | - | - | - | 8 | 62 |
| 154.000 | * | - | - | - | 8 | 61 |
| 157.000 | * | - | - | - | 8 | 60 |
| 157.000 | * | - | - | - | 8 | 59 |
| 161.000 | * | - | - | - | 8 | 58 |
| 161.000 | * | - | - | - | 8 | 57 |
| 161.000 | * | - | - | - | 8 | 56 |
| 161.000 | * | - | - | - | 8 | 55 |
| 161.000 | * | - | - | - | 8 | 54 |
| 162.000 | * | - | - | - | 8 | 53 |
| 167.000 | * | - | - | - | 8 | 52 |
| 168.000 | * | - | - | - | 8 | 51 |

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| Product-Limit Survival Estimates | | | | | | |
|---|---|---|---|---|---|---|
| exdy | | Survival | Failure | Survival Standard Error | Number Failed | Number Left |
| 168.000 | * | - | - | - | 8 | 50 |
| 169.000 | * | - | - | - | 8 | 49 |
| 171.000 | * | - | - | - | 8 | 48 |
| 174.000 | * | - | - | - | 8 | 47 |
| 175.000 | * | - | - | - | 8 | 46 |
| 175.000 | * | - | - | - | 8 | 45 |
| 175.000 | * | - | - | - | 8 | 44 |
| 176.000 | * | - | - | - | 8 | 43 |
| 176.000 | * | - | - | - | 8 | 42 |
| 177.000 | * | - | - | - | 8 | 41 |
| 179.000 | * | - | - | - | 8 | 40 |
| 179.000 | * | - | - | - | 8 | 39 |
| 181.000 | * | - | - | - | 8 | 38 |
| 182.000 | * | - | - | - | 8 | 37 |
| 182.000 | * | - | - | - | 8 | 36 |
| 182.000 | * | - | - | - | 8 | 35 |
| 182.000 | * | - | - | - | 8 | 34 |
| 182.000 | * | - | - | - | 8 | 33 |
| 183.000 | * | - | - | - | 8 | 32 |
| 184.000 | * | - | - | - | 8 | 31 |
| 184.000 | * | - | - | - | 8 | 30 |
| 185.000 | | 0.8659 | 0.1341 | 0.0447 | 9 | 29 |
| 185.000 | * | - | - | - | 9 | 28 |
| 185.000 | * | - | - | - | 9 | 27 |
| 186.000 | * | - | - | - | 9 | 26 |
| 187.000 | * | - | - | - | 9 | 25 |
| 188.000 | * | - | - | - | 9 | 24 |
| 188.000 | * | - | - | - | 9 | 23 |
| 188.000 | * | - | - | - | 9 | 22 |
| 189.000 | * | - | - | - | 9 | 21 |

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| Product-Limit Survival Estimates | | | | | | |
|---|---|---|---|---|---|---|
| exdy | | Survival | Failure | Survival Standard Error | Number Failed | Number Left |
| 189.000 | * | - | - | - | 9 | 20 |
| 190.000 | * | - | - | - | 9 | 19 |
| 191.000 | * | - | - | - | 9 | 18 |
| 192.000 | * | - | - | - | 9 | 17 |
| 193.000 | * | - | - | - | 9 | 16 |
| 195.000 | * | - | - | - | 9 | 15 |
| 196.000 | * | - | - | - | 9 | 14 |
| 196.000 | * | - | - | - | 9 | 13 |
| 196.000 | * | - | - | - | 9 | 12 |
| 196.000 | * | - | - | - | 9 | 11 |
| 196.000 | * | - | - | - | 9 | 10 |
| 196.000 | * | - | - | - | 9 | 9 |
| 196.000 | * | - | - | - | 9 | 8 |
| 197.000 | * | - | - | - | 9 | 7 |
| 197.000 | * | - | - | - | 9 | 6 |
| 203.000 | * | - | - | - | 9 | 5 |
| 206.000 | * | - | - | - | 9 | 4 |
| 206.000 | * | - | - | - | 9 | 3 |
| 207.000 | * | - | - | - | 9 | 2 |
| 209.000 | * | - | - | - | 9 | 1 |
| 215.000 | * | - | - | - | 9 | 0 |

| | |
|---|---|
| Patients withdrawing from the study, lost to follow-up or dying should be censored at the time of withdrawal/loss to follow-up/death.<br><br>All the above results should be provided in tabular form (see example from SAS below) showing for each event time: | All relevant data provided in tables above. |
| • time of event from baseline (days) | |
| • product-limit estimate of survival proportion | |
| • standard error of survival proportion | |

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| | |
|---|---|
| • number of patients failed | |
| • number of patients remaining at risk | |

| | | |
|---|---|---|
| B5. | **Priority question: Response rate definition.** Please provide a table of response rates from SANSIKA clinical trial for all the response rate definitions in the following table. | Provided below |

**Table B5.1 Response Rate: SANSIKA FAS - Imputed Data**

| Response definition | Ikervis response at 3 months | Vehicle response at 3 months | Ikervis response at 6 months | Vehicle response at 6 months |
|---|---|---|---|---|
| CFS better by 4, OSDI reduction >= 30% | 4.5% | 2.2% | 3.9% | 4.4% |
| CFS better by 3.5, OSDI reduction >= 30% | 0.6% | 1.1% | 1.3% | |
| CFS better by 3, OSDI reduction >= 30% | 7.1% | 5.5% | 13.6% | 3.3% |
| CFS better by 2, OSDI reduction >= 30% | 9.1% | 4.4% | 9.7% | 15.4% |
| CFS better by 1, OSDI reduction >= 30% | 7.1% | 8.8% | 7.8% | 11.0% |
| CFS unchanged, OSDI reduction >= 30% | 5.2% | 11.0% | 5.2% | 6.6% |

**Table B5.2 Response Rate: SANSIKA FAS - Observed Data**

| Response definition | Ikervis response at 3 months | Vehicle response at 3 months | Ikervis response at 6 months | Vehicle response at 6 months |
|---|---|---|---|---|
| CFS better by 4, OSDI reduction >= 30% | 4.2% | 2.2% | 3.8% | 4.7% |
| CFS better by 3.5, OSDI reduction >= 30% | 0.7% | 1.1% | 1.5% | |
| CFS better by 3, OSDI reduction >= 30% | 7.0% | 5.6% | 15.9% | 3.5% |
| CFS better by 2, OSDI reduction >= 30% | 9.9% | 4.5% | 11.4% | 15.1% |
| CFS better by 1, OSDI reduction >= 30% | 7.7% | 10.1% | 9.1% | 11.6% |
| CFS unchanged, OSDI reduction >= 30% | 4.2% | 10.1% | 3.8% | 5.8% |

| | | |
|---|---|---|
| B6. | The company reports that a systematic review carried out by the Cochrane collaboration found limited evidence on the efficacy of punctual plugs (company's submission, page 154). Please provide a reference for this publication. | Now provided. |

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| | | |
|---|---|---|
| B7. | There appears to be some inconsistency in the marking of confidential data in Table B41 and that in Table B46 in the company's submission. Please could you clarify these discrepancies? | Table B41 has been updated below |

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**Table B1 Deterministic sensitivity analysis**

| Parameter | Base case value | Lower limit | Upper limit |
|---|---|---|---|
| 3 month response probability (Ikervis) | 0.162 | 0.13 | 0.194 |
| 6 month response probability (Ikervis) | 0.188 | 0.15 | 0.226 |
| 3 month response probability (AT) | 0.077 | 0.061 | 0.093 |
| 6 month response probability (AT) | 0.077 | 0.061 | 0.093 |
| No response to temporary plugs | 0.0024 | 0.00192 | 0.0029 |
| Temporary plugs to permanent plugs | 0.1 | 0.08 | 0.12 |
| Treatment failure (Ikervis) | 0.109 | 0.087 | 0.138 |
| Treatment failure (AT) | 0.122 | 0.0976 | 0.1464 |
| Ikervis acquisition cost | £72 | £50 | £100 |
| Ikervis total cost | £110.67 | £88.53 | £132.80 |
| Vehicle acquisition cost | £0 | £0 | £5 |
| AT total cost | £44.40 | £35.52 | £53.28 |
| Non-responders AT cost | £88.63 | £70.90 | £106.35 |
| Temporary plugs cost | £628.95 | £503.16 | £754.74 |
| Permanent plugs cost | £628.95 | £503.16 | £754.74 |
| Post-surgery cost | £0 | £0 | £100 |
| Polyvinyl alcohol pack cost | £5.35 | £4.28 | £6.42 |
| Carbomers pack cost | £5.42 | £4.28 | £6.50 |
| Paraffin cost | £3.25 | £2.60 | £3.90 |
| Background AT cost (AT) | £44.40 | £35.52 | £53.28 |
| Background AT cost (Ikervis) | £38.67 | £30.94 | £46.04 |
| Background AT cost (temporary plugs) | £0 | £0 | £10 |
| Background AT cost (permanent plugs) | £0 | £0 | £10 |
| Background AT cost (non-responders) | £88.63 | £70.90 | £106.36 |
| AT drops per day | 14.64 | 11.712 | 17.568 |
| Ikervis drops per day | 12.68 | 10.144 | 15.216 |
| Temporary plugs drops per day | 0 | 0 | 10 |
| Permanent plugs drops per day | 0 | 0 | 10 |
| Non-responders drops per day | 29.78 | 23.824 | 35.736 |
| Drops per eye per day | 2 | 1 | 2 |
| Drops per eye per day (temporary plugs) | 2 | 1 | 2 |
| Drops per eye per day (permanent plugs) | 2 | 1 | 2 |
| No response utility | 0.66 | 0.656 | 0.664 |
| Response Utility | 0.738 | 0.669 | 0.806 |

| | |
|---|---|
| B8. Figures in Table B44 appear to not compute. Please could you | Table B44 has been updated |

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| | |
|---|---|
| clarify this? | below: |

**Table B44: Predicted resource use by cost category (post-hoc response definition)**

| Outcome | Ikervis + AT | AT alone | Incremental |
|---|---|---|---|
| Trial 0-3 months | £331 | £133 | £198 |
| Trial 3-6 months | £331 | £133 | £198 |
| Treatment responder | £1,080 | £160 | £920 |
| Temporary punctal plugs | £358 | £367 | -£9 |
| Permanent punctal plugs | £35 | £36 | -£1 |
| Non-responders | £21,406 | £21,942 | -£535* |
| Total (undiscounted) | £23,542 | £22,771 | £771 |
| Total (discounted) | £15,997 | £15,283 | £713 |

| | |
|---|---|
| B9. Please provide an analysis of SANSIKA response rates by Time Since Diagnosis, as specified in the table below: | Provided below |

**Table B9.1 Response Rate by Time Since Diagnosis: SANSIKA FAS - Imputed Data**

| | | CFS improvement >= 2 & OSDI improvement >= 30% | | | CFS improvement >= 3 & OSDI improvement >= 30% | | |
|---|---|---|---|---|---|---|---|
| Time since diagnosis | Treatment | Patients (n) | Responders (n) | Response rate (%) | Patients (n) | Responders (n) | Response rate (%) |
| Less than or equal to 12 months | Ikervis+AT(3 months) | 8 | 1 | 12.5 | 8 | 0 | - |
| | Ikervis+AT(6 months) | 8 | 2 | 25.0 | 8 | 1 | 12.5 |
| | Vehicle+AT(3 months) | 5 | 1 | 20.0 | 5 | 1 | 20.0 |
| | Vehicle+AT(6 months) | 5 | 2 | 40.0 | 5 | 0 | - |
| From 12 months to 24 months | Ikervis+AT(3 months) | 8 | 3 | 37.5 | 8 | 2 | 25.0 |
| | Ikervis+AT(6 months) | 8 | 4 | 50.0 | 8 | 2 | 25.0 |

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| | | CFS improvement >= 2 & OSDI improvement >= 30% | | | CFS improvement >= 3 & OSDI improvement >= 30% | | |
|---|---|---|---|---|---|---|---|
| Time since diagnosis | Treatment | Patients (n) | Responders (n) | Response rate (%) | Patients (n) | Responders (n) | Response rate (%) |
| | Vehicle+AT(3 months) | 3 | 1 | 33.3 | 3 | 1 | 33.3 |
| | Vehicle+AT(6 months) | 3 | 1 | 33.3 | 3 | 0 | - |
| Greater than 24 months | Ikervis+AT(3 months) | 137 | 29 | 21.2 | 137 | 17 | 12.4 |
| | Ikervis+AT(6 months) | 137 | 38 | 27.7 | 137 | 26 | 19.0 |
| | Vehicle+AT(3 months) | 83 | 10 | 12.0 | 83 | 6 | 7.2 |
| | Vehicle+AT(6 months) | 83 | 18 | 21.7 | 83 | 7 | 8.4 |
| Unknown | Ikervis+AT(3 months) | 1 | 0 | - | 1 | 0 | - |
| | Ikervis+AT(6 months) | 1 | 0 | - | 1 | 0 | - |

**Table B9.2 Response Rate by Time Since Diagnosis: SANSIKA FAS - Observed Data**

| | | CFS improvement >= 2 & OSDI improvement >= 30% | | | CFS improvement >= 3 & OSDI improvement >= 30% | | |
|---|---|---|---|---|---|---|---|
| Time since diagnosis | Treatment | Patients (n) | Responders (n) | Response rate (%) | Patients (n) | Responders (n) | Response rate (%) |
| Less than or equal to 12 months | Ikervis+AT(3 months) | 8 | 1 | 12.5 | 8 | 0 | - |
| | Ikervis+AT(6 months) | 6 | 2 | 33.3 | 6 | 1 | 16.7 |
| | Vehicle+AT(3 months) | 5 | 1 | 20.0 | 5 | 1 | 20.0 |
| | Vehicle+AT(6 months) | 4 | 2 | 50.0 | 4 | 0 | - |
| From 12 months to 24 months | Ikervis+AT(3 months) | 7 | 3 | 42.9 | 7 | 2 | 28.6 |
| | Ikervis+AT(6 months) | 7 | 4 | 57.1 | 7 | 2 | 28.6 |
| | Vehicle+AT(3 months) | 3 | 1 | 33.3 | 3 | 1 | 33.3 |

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| | | CFS improvement >= 2 & OSDI improvement >= 30% | | | CFS improvement >= 3 & OSDI improvement >= 30% | | |
|---|---|---|---|---|---|---|---|
| Time since diagnosis | Treatment | Patients (n) | Responders (n) | Response rate (%) | Patients (n) | Responders (n) | Response rate (%) |
| | Vehicle+AT(6 months) | 3 | 1 | 33.3 | 3 | 0 | - |
| Greater than 24 months | Ikervis+AT(3 months) | 122 | 27 | 22.1 | 122 | 15 | 12.3 |
| | Ikervis+AT(6 months) | 117 | 37 | 31.6 | 117 | 25 | 21.4 |
| | Vehicle+AT(3 months) | 81 | 10 | 12.3 | 81 | 6 | 7.4 |
| | Vehicle+AT(6 months) | 75 | 17 | 22.7 | 75 | 7 | 9.3 |
| Unknown | Ikervis+AT(3 months) | 1 | 0 | - | 1 | 0 | - |
| | Ikervis+AT(6 months) | 1 | 0 | - | 1 | 0 | - |

**Section C: Textual clarifications, references and additional points**

The ERG appreciates that the company has provided cited references on a separate disk. However, in addition:

| | | Response |
|---|---|---|
| C1. | **Priority request:** On page 51 of the company's submission it is stated that a full systematic review report is available on request. Please could you provide this? | Now provided |
| C2. | **Priority request:** Please also provide the full documents for the trial protocols and statistical analysis plans for SANSIKA and SICCANOVE. | Now provided |
| C3. | Not all references listed in the company's submission from page 210 onwards have an accompanying PDF/Word document. Please provide the relevant documents for the following reference: | |
| 34. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. | | Now provided. |

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| | |
|---|---|
| American Journal of Ophthalmology. [http://dx.doi.org/10.1016/S0002-9394%2803%2900218-6]. 2003;136(2):01. | |
| C4. In addition to the query raised in B6, a number of other references are cited throughout the company's submission without either the full citation or PDF/Word document provided. Please provide these for the following: | In addition to providing PDFs we have updated the reference list to include all references (provided at the end of the clarification questions*). |
| • Stern 1998 (see page 21 of company's submission) | Now provided. |
| • Nicols 2011 (see page 21 of company's submission) | Nichols 2011, provided |
| • National Health Service 2008 (see page 24 of company's submission) | Has since been updated to 2012 version (see below); originally taken from 2008 version. |
| • National Health Service 2014 (see page 24 of company's submission) | Should be 2012 not 2014; submission updated accordingly Nice. Dry Eye Syndrome. Clinical Knowledge Summary 2012 September. |
| • Nichols (see page 78 of company's submission) | Nichols 2002, now provided |
| • Rajagopalan (referred to numerous times, e.g. page 79 of company's submission) | Rajagopalan 2005, now provided |
| • EMEA/CHMP/SAWP/445808/2006 (see page 91 of company's submission) | Now provided |
| • McDonald 2010 (see page 165 of company's submission) | Now provided |
| • Koffler 2010 (see page 165 of company's submission) | Now provided |
| • Rajagopalan 2005 (see page 165 of company's submission) | Now provided |
| • Mertzanis 2005 (see page 165 of company's submission) | Now provided |
| • Data on file (see page 206 of company's | Now provided |

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| | submission) | |
| C5. | **Priority Question**: please provide a copy of the EPAR. If the EPAR is not yet finalised please provide the draft version. | Now provided |

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