

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Ciclosporin for treating dry eye disease

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UNIVERSITY OF
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IMPLEMENTATION
GROUP

The manufacturer identified eight issues in relation to factual errors in the original ERG report. Only two were considered to be factual errors by the ERG (clarification about the company's meta-analysis and model coding) resulting in changes being necessary to be made to the report. In addition the ERG identified minor errors which also resulted in minor changes to the ERG report. The pages of the report affected are presented here. Text that remains unaltered is greyed out.

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The ERG considers that, for two reasons, evidence from the SANSIKA trial is more relevant to the decision problem than evidence from the SICCANOVE trial. First, the whole SANSIKA trial population has severe DED but only a (non-randomised) sample of those recruited to the SICCANOVE trial has severe DED (17% or 50% of the population depending on the definition used). Second, the vehicle used in the SANSIKA trial is the proposed licensed Ikervis formulation (containing CKC), whereas the vehicle used in the SICCANOVE contained BAK.

With the exception of change in CFS, the ERG notes that none of the statistically significant differences between Ikervis and vehicle found from post-hoc analyses of SICCANOVE trial data were also found from analysis of SANSIKA trial data. Importantly, the primary outcome (CFS-OSDI) showed no statistically significant difference and so the relative clinical effectiveness of Ikervis compared to vehicle was not demonstrated. However, the ERG questions the relevance of this outcome for two reasons. First, it is not clear if the concept of a response formally defined by specific changes in only CFS and OSDI is clinically meaningful. Second, if it is accepted that the concept of response is clinically meaningful, then the issue is the lack of evidence available to support the use of any specified threshold value for this measure. The ERG is, therefore, unable to comment on whether the CFS-OSDI response as defined in SANSIKA (CFS improvement ≥ 2 and OSDI improvement $\geq 30\%$) or the CFS-OSDI response defined post-hoc (also using data from SANSIKA) and used to inform the economic model base case (CFS improvement ≥ 3 and OSDI improvement $\geq 30\%$), is most appropriate.

The ERG notes that the rates of eye irritation, eye pain and site irritation were higher in the SICCANOVE trial than in the SANSIKA trial; whilst rates of site pain were higher in the SANSIKA trial than in the SICCANOVE trial. However, overall, only a minority of patients experienced treatment-related AEs. These were mostly transitory and mild in severity and therefore the safety profile appears to be acceptable.

The ERG considers that the value of the evidence from the SANSIKA trial is limited by the fact that it uses the Ikervis vehicle as the comparator intervention, rather than any of the comparators specified in the NICE scope. Not only is the vehicle not commercially available, it is not currently used in routine clinical practice; in addition, the company argues that it may offer some therapeutic benefit. Certainly, improvements over time were reported for all efficacy outcomes in the vehicle arm of the SANSIKA trial. However, it is not clear whether the improvements occurred as a result of the vehicle, as a result of concomitant AT use, or as a combination of both vehicle and AT.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG is satisfied with the search strategy employed by the company to identify cost effectiveness studies, and is reasonably confident that no relevant published articles exist.

The ERG does not consider that the evidence available is sufficient to support a valid cost effectiveness analysis of Ikervis versus currently prescribed UK treatment options for severe DED. The economic model compares Ikervis plus AT versus AT and the model is largely populated with data from the SANSIKA trial. The results of the SANSIKA trial cannot be used directly in the model as the Ikervis vehicle is not a placebo, nor is it currently used in clinical practice. Instead, the company has made the assumption that the Ikervis vehicle and AT have the same efficacy.

The ERG has identified a number of issues relating to the data used to populate the model and/or how the data have been implemented. First, the model base case uses results from an analysis based on a post-hoc alteration to the primary outcome (i.e. ≥ 3 improvement in CFS and a 30% improvement in the OSDI). This leads to a more favourable ICER per QALY gained for Ikervis than if the pre-specified definition of the primary outcome had been used (≥ 2 improvement in CFS and a 30% improvement in the OSDI).

Second, the SANSIKA clinical study report (CSR) shows that trial discontinuations for any reason (16.2% versus 12.2%) are higher in the Ikervis group compared with those receiving vehicle. The company modellers have applied treatment costs in the first 6 months (i.e. the trial period) assuming that treatment is prescribed for 3 months at the beginning of each cycle. However, this takes no account of the small risk of patients dying or discontinuing treatment during a 3 month cycle.

Third, the company approach to modelling the utility effect of response to treatment is based on an assumption that improvement in HRQoL is not influenced by the treatment given and so HRQoL data are pooled across both arms of the SANSIKA trial. However, examination of the trial results indicates that a larger utility benefit is received by patients responding to treatment with vehicle than those who respond to Ikervis treatment. The effect of using the pooled utility results in the model is to eliminate the potential impact of any differences in patient experience due to the characteristics of the randomised treatment.

Other issues identified by the ERG are: incorrect AT usage calculations, incorrect discounting, naïve and inaccurate modelling of the age/sex profile of patients and insufficient variation in the trial outcome parameter values used in the PSA.

from -£2 to + £5,864. If all of the ERG amendments are applied, the ICER per QALY gained increases from £19,156 (company's estimate) to **£53,378**.

The ERG's changes to the alternative base case (which utilises the pre-specified SANSIKA trial definition of the primary outcome) lead to changes in the ICER per QALY gained for the comparison of Ikervis plus AT with vehicle plus AT that range from Ikervis being dominated to an increase in the ICER of + £99,999. If all of the ERG amendments are applied then Ikervis plus AT is dominated by vehicle plus AT, i.e. treatment with vehicle plus AT generates more utility gain than treatment with Ikervis plus AT.

in the draft EPAR.³⁵ Additional meta-analyses were also provided during the clarification process. Only the meta-analyses presented in the CS for the subgroup of patients with severe DED and Sjögren's syndrome (severe FAS) are considered relevant to the decision problem by the ERG. During the factual error checking process, the company also clarified that the meta-analysis was conducted at the individual patient data level (with the initial raw data) thus weighting the studies according to their size and maintaining randomisation.

AE data were also pooled to assess safety. During the clarification process, the company confirmed that no specific meta-analysis model was used for the analysis and descriptive statistics were provided. However, the ERG also notes the data presented include an estimate for relative risk between treatment arms, implying statistical analyses were conducted that were not simply descriptive.

4.2.5 Risk of bias

As recommended by the Cochrane Collaboration,⁴⁷ the company conducted assessments of the risk of bias for the SANSIKA and SICCANOVE trials. These assessments are presented in Table B9 of the CS (page 95) and summarised in Table 6. The ERG concurs with the company's risk of bias conclusions and agrees that both the SANSIKA and SICCANOVE trials have a low risk of bias. It is noted that while an ITT analysis was not used in either trial, the FAS was used in both trials. As explained in section 4.2.4, the FAS was almost identical to the intention to treat ITT population which is considered the ideal for RCTs as it includes all randomised patients. However, as also noted in section 4.2.4, only a non-randomised sample of patients with severe DED in SICCANOVE are relevant to the decision problem.

discontinue treatment (4.6% per 3 months), with no evidence of any initial excess of patients discontinuing. When these parameter values are applied to the company model the ICER increases to £25,020 per QALY gained; this is the ERG's preferred option.

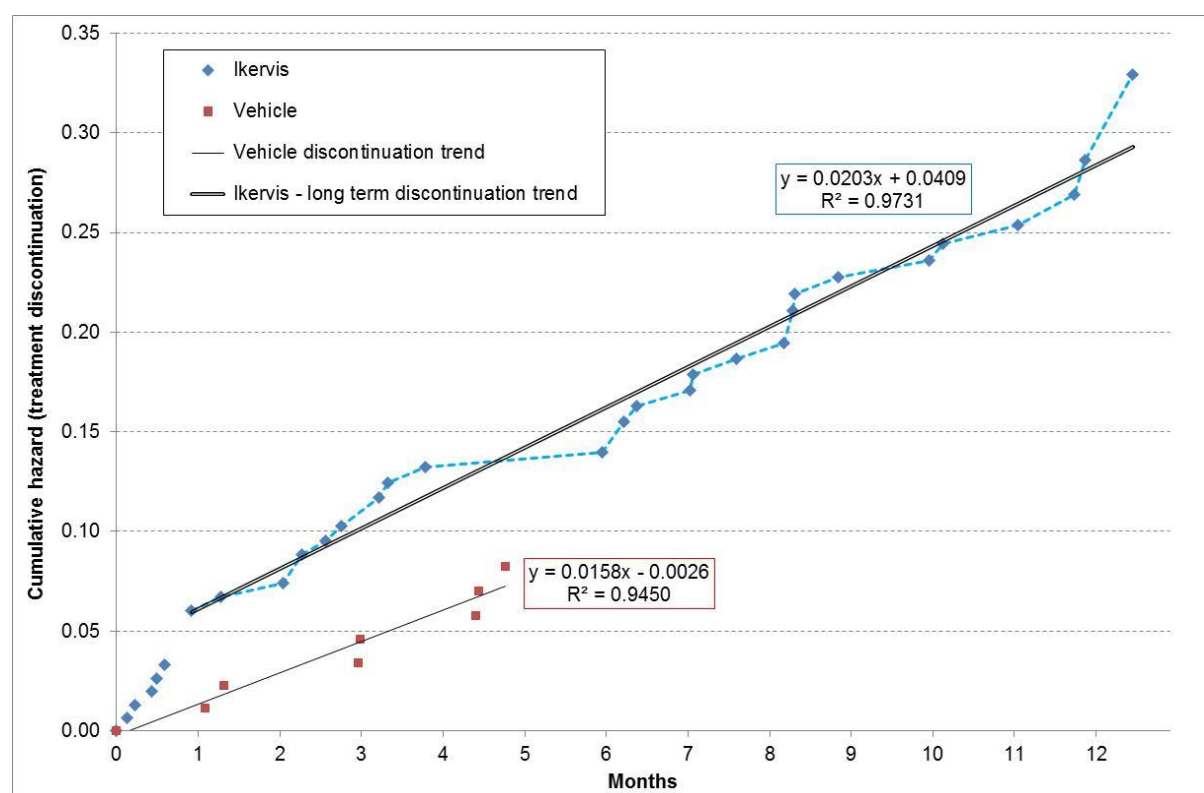


Figure 5 Cumulative hazard trends in SANSIKA trial discontinuation of treatment data

5.5.7 Artificial tear use error

The ERG has identified an inconsistency between the calculation of AT use at baseline and at 6 months. The company has argued that there is no basis for distinguishing between the number of drops per eye per day recorded in the two trial arms (16.54 for the vehicle arm and 13.24 in the Ikervis arm) as the difference is not statistically significant. However the difference recorded at 6 months is much smaller (7.32 and 6.34 respectively) and is also not statistically significant. Moreover, the proportionate reduction in AT use is very similar in the two trial arms (55.7% in the vehicle arm and 52.1% in the Ikervis arm). There is therefore no basis for employing different AT use estimates for patients responding to treatment in either arm. If an average usage of 6.83 drops per eye per day is applied to the model, the ICER for Ikervis vs vehicle increases to **£36,307** per QALY using the SANSIKA protocol definition of response, and to **£20,950** per QALY using the company's post hoc definition.

5.5.8 Model coding errors

Section deleted following the factual error checking process.

The model submitted by the company is framed around evidence from the SANSIKA trial, but uses as base case a post-hoc alteration to the key outcome definition which substantially improves the estimated ICER in favour of Ikervis. The ERG has identified several problems with the implementation of the model, and the use made of SANSIKA results to populate the model. The ERG has sought to rectify errors and improve the calibration of key parameter values wherever possible.

The ERG concludes that, even if the model were to be accepted as a basis for decision-making, implementation of the ERG amendments leads to the estimated base case ICER per QALY gained being considerably greater than that presented in the CS.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

This section shows the impact on the ICER per QALY gained of changes made by the ERG to the company model. Due to issues outlined in section 5.5.1 relating to the lack of evidence to address the decision problem, the resultant figures should not be understood to be any expression of support for the validity of the model.

A detailed summary of the various model corrections and amendments identified and implemented by the ERG is shown in Table 25. This includes results for both definitions of response to treatment – the SANSIKA trial primary outcome measure (at least 2 point improvement on CFS scale and 30% improvement in OSDI), and the post-hoc measure (at least 3 point CFS improvement and 30% improvement in OSDI).

The two most influential ERG changes are the use of treatment discontinuation rates estimated directly from SANSIKA Kaplan-Meier results, and the use of differential utility values for treatment responders sourced from the SANSIKA trial results.

Of secondary importance to the estimation of the ICER are the correction of erroneous parameter values for AT use, and the revision of treatment costs to reflect monthly prescribing.

The possibility that the trial population includes some more recently diagnosed patients whose condition may be more amenable to non-CsA treatments cannot be resolved from the limited trial evidence currently available. If confirmatory evidence is obtained, then limiting CsA-based treatment to more established severe DED would result in better relative effectiveness for Ikervis, though the extent of effect on the estimated ICER cannot be estimated with any confidence.

Table 25 Cost effectiveness results for Ikervis versus vehicle with ERG revisions to company's base case comparison

Model scenarios & ERG revisions	Ikervis + AT		Vehicle + AT		Incremental		ICER	ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change
A. Company's base case (Post-hoc response)	£15,997	9.744	£15,283	9.707	£713	0.037	£19,156	-
R1. Age/sex modelling	£15,238	9.277	£14,533	9.241	£705	0.036	£19,382	+ £226
R2. Treatment discontinuation	£15,990	9.742	£15,245	9.713	£746	0.030	£25,020	+ £5,864
R3. Treatment costs	£16,181	9.744	£15,365	9.707	£816	0.037	£21,916	+ £2,760
R4. Responder utility	£15,997	9.763	£15,283	9.733	£713	0.029	£24,473	+ £5,317
R5. Artificial tears use	£16,038	9.744	£15,257	9.707	£780	0.037	£20,950	+ £1,795
R6. Discounting	£16,206	9.872	£15,483	9.834	£723	0.038	£19,153	- £3
B. Applying R1-R6	£15,664	9.414	£14,735	9.397	£929	0.017	£53,378	+ £34,222
C. Alternative base case (SANSIKA response)	£16,132	9.788	£14,987	9.754	£1,145	0.034	£33,291	-
R1. Age/sex modelling	£15,370	9.320	£14,244	9.287	£1,126	0.033	£33,625	+ £334
R2. Treatment discontinuation	£16,043	9.762	£14,987	9.754	£1,056	0.008	£133,290	+ £99,999
R3. Treatment costs	£16,293	9.788	£15,058	9.754	£1,235	0.034	£35,915	+ £2,624
R4. Responder utility	£16,132	9.754	£14,987	9.782	£1,145	-0.027	DOM	-
R5. Artificial tears use	£16,191	9.788	£14,942	9.754	£1,249	0.034	£36,307	+ £3,016
R6. Discounting	£16,343	9.916	£15,183	9.881	£1,160	0.035	£33,290	£0
D. Applying R1-R6	£15,786	9.406	£14,329	9.458	£1,457	-0.052	DOM	-

QALYs = quality adjusted life years; DOM = dominated (more costly and less effective)

In terms of the cost effectiveness results, one major problem with deriving any conclusions again lies with the lack of any comparison with other CsA formulations. As such, the ERG considers that only a cost minimisation analysis comparing Ikervis to Restasis and two alternative unlicensed CsA formulations (CsA 2% eye drops and Optimune 0.2% ointment) is possible. However, this requires an assumption that the treatments being considered are of equivalent efficacy, are associated with similar AEs and incur similar administration, prescribing and monitoring costs. As noted above, such assumptions cannot be robustly supported or refuted.

Nevertheless, the ERG has attempted to address key issues with the company's model where possible. By doing so, the ERG estimates that the ICER is higher than £50,000 per QALY gained when response to treatment is based on a post-hoc composite endpoint (CFS improvement ≥ 3 and OSDI improvement $\geq 30\%$) as opposed to the company's estimate of £19,156. When the composite endpoint that was the pre-specified primary outcome for SANSIKA is used (CFS improvement ≥ 2 and OSDI improvement $\geq 30\%$), the ERG shows that Ikervis plus AT is dominated by AT (whereas the company's ICER is £33,291 per QALY gained). However, the important structural problem with implementation of the model design is too far-reaching for the ERG to correct without rebuilding core sections of the model. Extreme caution must therefore be taken when attempting to interpret the company's and ERG's cost effectiveness results.

8 OVERALL CONCLUSIONS

The ERG draws the following conclusions:

- Clinical evidence from the pivotal SANSIKA trial does not demonstrate significant differences between Ikervis and vehicle for the majority of outcomes measured, including the primary outcome measured in this trial, despite such differences being apparent in the results of the post-hoc analyses of patients with severe DED in the supportive SICCANOVE trial. Improvements over time were however observed for the majority of outcomes in both trial arms in both trials. Only a minority of patients who received Ikervis reported treatment-related AEs and the safety profile is therefore acceptable.
- A comparison of Ikervis with other CsA formulations is more appropriate for evaluating both clinical and cost effectiveness than a comparison with vehicle (or, by proxy, AT) since vehicle is not used, or commercially available, for treating severe DED in clinical practice in England.
- However, a current lack of (direct or indirect) clinical evidence precludes a reliable, or robust, clinical comparison of Ikervis with any the other CsA formulations currently in use (off-label) in clinical practice in England.
- Clinical efficacy from the pivotal SANSIKA trial utilises CFS-OSDI response as the primary outcome in which response is defined as an improvement of CFS ≥ 2 and OSDI $\geq 30\%$. A post-hoc analysis is utilised for the company's base case economic model in which response is defined as CFS ≥ 3 and OSDI $\geq 30\%$. While changes in CFS and OSDI are considered valid outcomes for measuring signs and symptoms associated with DED, the ERG is unaware of evidence to support the use of a composite CFS-OSDI endpoint as a robust and reliable measure of efficacy (regardless of the threshold used for CFS improvement).
- Using the post-hoc analysis of CFS-OSDI response from the SANSIKA trial the company's economic base case generates an ICER per QALY gain of £19,156 for Ikervis plus AT versus AT; however, using the SANSIKA trial pre-specified primary outcome results in an ICER per QALY gained of £33,291 for Ikervis plus AT versus AT.
- Six ERG amendments to the model utilising preferred alternative parameter values result in an ICER per QALY gained of **£53,378** for Ikervis plus AT versus vehicle plus AT using the post-hoc definition of CFS-OSDI response, whereas Ikervis plus AT is dominated by vehicle plus AT (leads to fewer QALY gains and is more costly) when using the pre-specified primary outcome for the SANSIKA trial.
- Given the lack of (direct or indirect) clinical evidence for Ikervis compared with other CsA formulations, and given problems with the reliability of the company's cost effectiveness analyses, the ERG advocates a cost minimisation analysis for comparing Ikervis with other CsA formulations. This assumes equivalent clinical effectiveness of all CsA formulations and shows Ikervis to be less costly than Restasis but more costly than the two other CsA formulations currently in use in clinical practice (Optimmune 0.2% [ointment] and 2% CsA drops).

10.3 Appendix 3: Implementation of ERG decision model amendments

Model amendments implemented by the ERG are activated by a series of modification logic switches; these take the value 0 when the original model logic is active, and positive integer values (1, 2,...,n) when alternative values or assumptions are active. The logic switches are labelled Mod_1 to Mod_7 (Mod_3 was exploratory but is not used by ERG as it has no impact on any model ICERs, and is not described here).

1. USE ANNUAL DISCOUNTING INSTEAD OF CONTINUOUS DISCOUNTING (Mod_1)

Create range name Mod_1 (binary integer variable taking values 0 or 1)

On Sheets 'Ikervis Trace' and 'Artificial Tears Trace'

Enter formula in cell E10 as follows:

= INT(C10/12)

Copy formula in cell E10 to range (E11:E130)

Amend formula in cell AD11 as follows:

= AC11*(1/(1 + c.DiscRate)^IF(Mod_1 = 0,D11,E11))

Copy formula in cell AD11 to range (AD12:AD130)

Amend formula in cell AM11 as follows:

= AL11*(1/(1 + u.DiscRate)^IF(Mod_1 = 0,D11,E11))*AN11

Copy formula in cell AM11 to range (AM12:AM130)

2. USE ALTERNATIVE TREATMENT DISCONTINUATION RATES (Mod_2)

Create range name Mod_2 (integer variable taking values 0, 1 or 2)

On Sheet 'Transition Matrix'

Enter values in cells as follows:

Cell F37 = 0.162

Cell F38 = 0.122

Cell AF42 = 0.0589490

Cell AF43 = 0.0461775

Enter formulae in cells as follows:

Cell G35 = IF(Mod_2 = 0, D35/C35, 0.162)

Cell G36 = IF(Mod_2 = 0, D36/C36, 0.122)

Cell AC42 = IF(Mod_2 = 2, AF42, 1-EXP(-AB42 * 3))

Cell AC43 = IF(Mod_2 = 2, AF43, 1-EXP(-AB43 * 3))

3. USE SEPARATE AT USE RATES IN TRIAL ARMS & CORRECT PARAMETER VALUE ERRORS (Mod_4)

Create range name Mod_4 (binary integer variable taking values 0 or 1)

On Sheet 'Cost and resource use'

Enter formulae in cells as follows:

Cell D38 = IF(Mod_4 = 0, 7.32, (7.32+6.34)/2)

Cell D39 = IF(Mod_4 = 0, 6.34, (7.32+6.34)/2)

4. USE STANDARD ERROS FROM DATA SOURCES FOR PSA (Mod_5)

Create range name Mod_5 (binary integer variable taking values 0 or 1)

On Sheet 'Cost and resource use'

Enter formulae in cells as follows:

Cell Z18 = 0.0395

Cell Z19 = 0.0446

Cell Z20 = Z21

Cell Z21 = ((Z18*AA18) + (Z19*AA19))/(AA18 + AA19)

Cell AB18 = IF(Mod_5 = 0, AA18/10, AA18*Z18)

Copy formula in Cell AB18 to Range AB19:AB21

On Sheet 'Transition Matrix'

Enter formulae in cells as follows:

Cell AB23 = IF(Mod_5 = 0, AA23/10, AA23*0.2)

Cell AB24 = IF(Mod_5 = 0, AA24/10, AA24*0.18)

Cell AB25 = IF(Mod_5 = 0, AA25/10, AA25*0.39)

Cell AB26 = IF(Mod_5 = 0, AA26/10, AA26*0.39)

5. USE STANDARD ERROS FROM DATA SOURCES FOR PSA (Mod_6)

Create range name Mod_6 (binary integer variable taking values 0 or 1)

On Sheet 'Ikervis Trace'

Enter formulae in cells as follows:

Cell S11 = S\$3*CycleLength*IF(Mod_6 = 0, F11, (2*F10 + F11)/3)*AN11

Cell T12 = T\$3*CycleLength*IF(Mod_6 = 0, G12, (2*F11 + G12)/3)*AN12

Cell U13 = U\$3*CycleLength*IF(Mod_6 = 0, H13, (2*G12 + H13)/3)*AN13

Cell U14 = U\$3*CycleLength*IF(Mod_6 = 0, AVERAGE(H13:H14), (2*H13 + H14)/3) *AN14

Copy formula in Cell U14 to Range U15:U130

On Sheet 'Artificial Tears Trace'

Enter formulae in cells as follows:

Cell V11 = V\$3*CycleLength*IF(Mod_6 = 0, I11, (2*I10 + I11)/3)*AN11

Cell W12 = W\$3*CycleLength*IF(Mod_6 = 0, J12, (2*I11 + J12)/3)*AN12

Cell X13 = X\$3*CycleLength*IF(Mod_6 = 0, K13, (2*J12 + K13)/3)*AN13

Cell X14 = X\$3*CycleLength*IF(Mod_6 = 0, AVERAGE(K13:K14), (2*K13 + K14)/3)*AN14

Copy formula in Cell X14 to Range X15:X130

6. USE TREATMENT SPECIFIC RESPONSE-RELATED UTILITY VALUES (Mod_7)

Create range name Mod_7 (binary integer variable taking values 0 or 1)

On Sheet 'Utilities'

Create a table of utility values as follows:

Cell M10 = u.NoResponse Copy Cell M10 to Range N10:P10

Cell M11 = 0.055

Cell N11 = 0.104

Cell O11 = 0.097

Cell P11 = 0.135

Cell M9 = M10 + M11 Copy Cell M9 to Range N9:P9

On Sheet 'Ikervis Trace'

Enter formulae in cells as follows:

Cell AL11 = (AI11*IF(Mod_7 = 0,u.Response,IF(posthoc = 0,Utilities!\$M\$9,Utilities!\$O\$9)) + AJ11*u.NoResponse)*(CycleLength/12)

Copy formula in Cell AL11 to Range AL12:AL130

On Sheet 'Artificial Tears Trace'

Enter formulae in cells as follows:

Cell AL11 = (AI11*IF(Mod_7 = 0,u.Response,IF(posthoc = 0,Utilities!\$N\$9,Utilities!\$P\$9)) + AJ11*u.NoResponse)*(CycleLength/12)

Copy formula in Cell AL11 to Range AL12:AL130

7. AGE/SEX/EVENT POPULATION WEIGHTED AVERAGE RESULTS

This modification to the company model requires use of a new VBA macro **GetICER** (activated by pressing **Ctrl + Shift + I**). The calculations are carried out in a new worksheet (ByAge) which is included in the ERG modified version of the model, together with the new macro code.

On Sheet 'Inputs',

Enter formulae in cells as follows:

Cell W4 = ByAge!A2

Cell W5 = ByAge!B2

On Sheet 'Mortality',

Enter formulae in cells as follows:

Cell F11 = C11*MalePropn + D11*(1-MalePropn)

Copy formula in Cell F11 to Range F12:F111

VBA macro GetICER

```
Sub GetICER()  
,  
' GetICER Macro  
' Run through a set of age and gender scenarios and copy and paste the resulting ICER.  
,  
' Keyboard Shortcut: Ctrl+Shift+I  
,  
Dim i As Integer  
  
Application.ScreenUpdating = False  
  
Sheets("ByAge").Select  
  
    Range("A4").Activate  
  
    For i = 1 To 34  
        Set m = ActiveCell  
        m.Range("A1:B1").Select  
        Selection.Copy  
        Range("A2:C2").Select  
        Selection.PasteSpecial Paste:=xlPasteValuesAndNumberFormats, Operation:= _  
            xlNone, SkipBlanks:=False, Transpose:=False  
        Range("E2:K2").Select  
        Application.CutCopyMode = False  
        Selection.Copy  
        m.Offset(0, 4).Range("A1").Select  
        Selection.PasteSpecial Paste:=xlPasteValuesAndNumberFormats, Operation:= _  
            xlNone, SkipBlanks:=False, Transpose:=False  
        m.Offset(1, 0).Range("A1").Select  
    Next i  
  
Sheets("ByAge").Select  
    Range("A2").Value = 61  
    Range("B2").Value = 0.5  
  
Sheets("ByAge").Select  
  
    Range("A39").Activate  
  
Application.ScreenUpdating = True  
  
End Sub
```