PharmaMar comments

Issue: the TAG assumptions on allergic reaction probability as a parameter within the base-case economic analysis

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Result of amended model or expected impact on the result (if applicable)</th><th>BMJ-TAG response</th></tr>
<tr>
<td>Within Table 108 (pg 276) of the Assessment Report, the TAG outlines the probability of allergic reactions for each treatment which are parameters used in the base-case economic analysis.

The TAG estimates probability of an allergic reaction with PLDH at 5.0%, which is identical to the estimated probability of an allergic reaction with trabectedin plus PLDH. These estimated probabilities have been sourced from clinical opinion.

A lower dose of PLDH is used when administered with the combination of trabectedin compared to when PLDH is administered as a monotherapy. Therefore the allergic reaction associated with PLDH would be lower in the combination arm compared to the PLDH monotherapy arm.

This was observed as part of the results in OVA-301. The allergic reactions measured as part of the trial are outlined below: [Data on file]
<table>
<tr><th>Allergic reaction</th><th>PLDH, n (%)</th><th>Trabectedin plus PLDH, n (%)</th></tr>
</table>
</td>
<td>PharmaMar suggests that the TAG update the base-case economic analysis to account for the reduced probability of allergic reactions in the trabectedin plus PLDH and PLDH monotherapy arms.

The suggested probability for allergic reaction is 2% with trabectedin plus PLDH (cell C73 to equal 0.02 on sheet ‘Model parameters, ranges &dists’) and 4% for PLDH (cell C72 to equal 0.04 on sheet ‘Model parameters, ranges &dists’)</td>
<td>On sheet ‘Engine (PLDH vs. Trab)’, cell FR10 the ICER has changed from £35,646 to £35,638.</td>
<td>The TAG model was constructed using data available at the time. In the absence of consistent data to inform estimates of the probability of allergic reaction, the TAG used expert clinical opinion. The TAG thanks the manufacturer for the new data submitted here, and notes that according to the manufacturer’s analysis, the impact of incorporating these data on the TAG’s ICER estimates is small.</td>
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</table>

Hypersensitivity	12 (4)	8 (2)	based on hypersensitivity reactions observed in OVA-301.		
Drug hypersensitivity	4 (1)	1 (<1)			
Anaphylactic reaction	2 (1)	0 (0)			
When trial results are available these should be used in preference to clinical opinion; in this case, hypersensitivity is a preferred outcome to measure the probability of allergic reactions. The results of OVA-301 are clearly different to the results estimated by clinical opinion, and we would strongly recommend trial results are assumed in the base case analysis.					

Issue: the TAG assumes that differences in dosing schedules between UK clinical practice and the OVA-301 study will not affect the effectiveness of trabectedin plus PLDH or PLDH monotherapy

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	BMJ-TAG response
The TAG comments: *"….as a sensitivity analysis, the TAG used head-to-head PFS and OS data estimated by the manufacturer within the TAG model to assess the resultant ICER. The ICER estimated by the TAG in this exploratory analysis was £35,646 per additional QALY. This figure compares with the manufacturer*	PharmaMar request that the TAG amend the model such that the dosing for trabectedin plus PLDH and PLDH	The effect of changing the dosing assumptions within the BMJ model has been explored. On the	The TAG thanks the manufacturer for their comments. In summary, the manufacturer asserts that the TAG may have overestimated the incremental cost of trabectedin plus PLDH versus PLDH as a result of: 1. overestimating the cost of trabectedin plus PLDH; 2. underestimating the cost of PLDH monotherapy.

estimate of £27,573 for the same comparison. The difference in ICER estimated between the TAG model and the manufacturer's model was a result of a difference in estimated incremental QALYs, rather than the difference in incremental costs. The TAG believes that this may be due to the manufacturer's method of discounting future costs and benefits; an area in which the ERG for TA222 previously raised concerns." (pg 33) Following investigation of the effect of discounting (see Issue 4 in PharmaMar's response to the TAG Assessment Report), we believe that the difference in the ICERs obtained (£35,646 vs. £27,573) are primarily due to the dosing assumptions of trabectedin and PLDH used in the base case for the manufacturer's and BMJ-TAG models. When calculating drug costs the TAG uses the licensed dose for trabectedin plus PLDH (1.1 mg/m^2 and 30 mg/m^2 respectively) and an unlicensed dose; based on expert opinion for PLDH monotherapy (40 mg/m^2). In comparison, the manufacturer's model calculates drug costs based on the mean total dose per patient, recorded for OVA-301 platinum-sensitive patients. These doses are as follows; trabectedin plus PLDH (1 mg/m^2 and 27.43 mg/m^2 respectively) and PLDH monotherapy (44.95 mg/m^2). Of most importance, is determining which is the correct dose to employ in this head-to-head comparison of trabectedin plus PLDH vs. PLDH. To evaluate this, one must consider the inherent assumptions of the two approaches. The TAG model assumes the licensed dose of trabectedin (1.1 mg/m^2) plus PLDH (30 mg/m^2) is used to calculate drug costs for the trabectedin plus PLDH arm. On the other hand, the unlicensed dose of 40 mg/m^2 (instead of the licensed 50 mg/m^2) is used to	monotherapy are based on OVA-301 average doses so that both outcomes and costs are consistently evaluated (this amendment is described in the 'Description of problem' column). The following wording for the assessment report is suggested: "When the mean doses of trabectedin plus PLDH, and PLDH from the OVA-301 study are applied over a 50 year time horizon in the TAG model, the ICER reduces from £35,646 to £27,886 which is similar to that seen in the manufacturer's submitted model (£27,573). When a 15 year time horizon is applied, the ICERs for the TAG model and amended manufacturer's model with cyclic	'Drug cost calculations' sheet the following changes have been made: • Cell AJ75 has been changed from 40 to 44.95 • Cell BA75 has been changed from 1.1 to 1 • Cell BD75 has been changed from 30 to 27.43 On sheet 'Engine (PLDH vs. Trab)', cell FR10, the ICER has changed from £35,646 to £29,409 over a 15 year time horizon. Increasing the time horizon to 50 years (cell E11 in Parameters (4)) reduces the ICER to £27,886. Please note, TAG ICERs incorporate the new rates for	In addition, the manufacturer asserts that the overestimation of incremental costs drives the difference between the TAG's and manufacturer's estimates of the head-to-head ICERs of trabectedin plus PLDH versus PLDH monotherapy. **Overestimating the cost of trabectedin plus PLDH** The manufacturer considers that the TAG has overestimated the cost of trabectedin plus PLDH by using a higher dose of trabectedin plus PLDH in the TAG economic model when compared with the average doses of trabectedin plus PLDH in OVA-301. The TAG considers that both the manufacturer's model and the TAG's model estimate trabectedin plus PLDH cost based on the average dose. However, due to the differences in model structure, the average dose is not explicitly stated in the TAG model. The TAG believes this may have given rise to confusion. For the manufacturer's model structure, mean parameters were required. Time was not explicitly modelled. Costs and QALYs associated with each health state were applied to the mean time in that health state. The manufacturer therefore used the mean drug dose to estimate mean drug cost. In the model developed by the TAG, mean times to progression and death were not explicitly modelled. This is because the TAG used an area under the curve approach. To estimate the cost of trabectedin plus PLDH, intended drug dose (and therefore drug cost) was applied for each cycle, for the patients remaining in the progression-free health state. Over the six cycles, this gives rise to an average dose below the intended dose, because fewer patients remain in the progression-free health state in subsequent months. The average dose of trabectedin plus PLDH, when estimated across the six cycles of therapy in the TAG base case model, is similar to the average dose applied in the

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<td>calculate drug costs for single agent PLDH. This is based on clinical expert advice:

“The licensed dose of PLDH when given as a monotherapy is 50 mg/m^2 given intravenously once every 4 weeks for as long as disease does not progress and the patient continues to tolerate treatment;[27] clinical expert advice is that typical UK clinical practice is to administer PLDH at a dose of 40 mg/m^2.” (pg 47, 283)

This assumption causes two issues. Firstly, it promotes the use of unlicensed dosing schedules for PLDH, which may create a conflict with NICE guidelines and the NICE scope whereby only licensed indications (and therefore the doses that are stated as being licensed in the Summary of Product Characteristics) are considered for this evaluation. Indeed, the final scope of the MTA has the appraisal objective of:

“To appraise the clinical and cost effectiveness of topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine within their licensed indications for the treatment of recurrent ovarian cancer [NICE 2012].”

Secondly, in using the patient level data from the platinum-sensitive population to calculate PFS and OS for PLDH, the TAG assumes that the lower 40 mg/^{2} dosing schedule will provide the same effectiveness in terms of PFS and OS benefits, as that observed with a higher PLDH dosing schedule (44.95 mg/m^2) in the OVA-301 study. Similarly, in using the patient level data from the platinum-sensitive population to calculate PFS and OS for trabectedin plus PLDH, the TAG assumes that the higher dosing schedules (1.1 mg/m^2 for trabectedin and 30 mg/m^2 for PLDH) will provide the same effectiveness in terms of PFS and OS benefits, as</td>
<td>discounting are £29,409 and £29,884 respectively.”

Please note, TAG ICERs incorporate the new rates for allergic reactions (see Issue 1).</td>
<td>allergic reactions (see Issue 1).</td>
<td>manufacturer’s model.

Table 1. Average drug dose per patient m^2
<table>
<tr><th></th><th colspan="2">PharmaMar</th><th colspan="2">TAG</th></tr>
<tr><th></th><th>Trabectedin</th><th>PLDH</th><th>Trabectedin</th><th>PLDH</th></tr>
<tr><td>Average dose per patient (mg/m^2)</td><td>1.0</td><td>27.43</td><td>1.0</td><td>28.38</td></tr>
<tr><td>Total drug cost estimated (no PAS)</td><td colspan="2">£21,734</td><td colspan="2">£20,878</td></tr>
<tr><td>Total drug cost (with PAS)</td><td colspan="2">£15,388</td><td colspan="2">£17,604</td></tr>
</table>

In the sensitivity analysis of the TAG model carried out by the manufacturer, the intended drug dose (1.1 mg/m^2 for trabectedin and 30 mg/m^2 for PLDH) was replaced by the average drug dose from OVA-301 (1 mg/m^2 for trabectedin and 27.43 mg/m^2 for PLDH). As a result of the TAG model structure, the consequence of the manufacturer’s changes is to lower the average modelled dose to 0.95 mg/m^2 for trabectedin and 25.95 mg/m^2 for PLDH.

The TAG does not consider the manufacturer’s adjustments to be correct and believes they are likely to underestimate average dose (and therefore cost) of trabectedin plus PLDH within the TAG model.</td>
</tr>
</table>

that observed with a lower dosing schedules (1 mg/m^2 for trabectedin and 27.43 mg/m^2 for PLDH) in the OVA-301 study. Both of these assumptions are to the disadvantage of the trabectedin plus PLDH arm. On the other hand, the manufacturer's model calculates drug costs for trabectedin plus PLDH and PLDH monotherapy based on the observed dosing schedules from the OVA-301 study. **Consequently, PFS and OS calculated in the model are reflective of the dosing schedules used.** Although these dosing schedules may not be in line with clinical practice in the UK, a more reasonable assumption would be that if the UK dosing schedules were to be used then effectiveness would be affected proportionally (with either increased or reduced doses in the trabectedin plus PLDH arm or PLDH arm, respectively). Hence, one would expect that the cost-effectiveness results in the manufacturer's model (which assumes dosing and effects from the OVA-301 study) would not change if the dosing were to be more aligned with UK clinical practice. Therefore we believe the most appropriate and consistent way to compare the clinical (efficacy and safety), and cost effectiveness is to use the outcomes that were obtained from the patient level data using the mean dose that patient's received in the OVA-301 study. The effect of changing the dosing assumptions within the BMJ model has been explored. On the 'Drug cost calculations' sheet the following changes have been made: • Cell AJ75 has been changed from 40 to 44.95 • Cell BA75 has been changed from 1.1 to 1			**Underestimating the cost of PLDH monotherapy** The TAG acknowledges that the costs associated with PLDH monotherapy used in the TAG sensitivity analysis of head-to-head data, are based on the dose expected to be used in clinical practice. The rationale for assessing the cost of regimens likely to be used in clinical practice was based on expert clinical opinion that the efficacy of PLDH monotherapy is likely to be equivalent at 40 mg/m^2 and 50 mg/m^2. However, the TAG acknowledges the limitation of this assumption and consequently carried out a scenario analysis (of the base case analysis) in which the intended dose of 50 mg/m^2 was used to calculate PLDH monotherapy costs (note – the average dose of PLDH given an intended dose of 50 mg/m^2 was 44.10 mg/m^2, which is similar to the manufacturer's estimate of 44.95 mg/m^2). In this scenario, as described within the Assessment Report, the deterministic ICER for trabectedin plus PLDH versus PLDH fell from £85,212 to £77,290 (with PAS). For completeness, the TAG carried out a further analysis on the scenario analysis in which head-to-head data were used to compare trabectedin plus PLDH versus PLDH monotherapy. In this scenario, the intended dose of PLDH monotherapy was increased to 50 mg/m^2 (average dose 44.10 mg/m^2). The ICER fell from £35,646 to £32,289 (with PAS). **Overestimation of incremental costs as an explanation for the difference in TAG and manufacturer head-to-head ICERs** Based on the aforementioned inaccuracies in the manufacturer's sensitivity analysis of the TAG model, the TAG considers that the approach to drug cost calculations used in the TAG model is not responsible for the difference between the TAG's and manufacturer's head-to-head ICERs.

• Cell BD75 has been changed from 30 to 27.43 Then by referring to sheet 'Engine (PLDH vs. Trab)', cell FR10 the ICER has changed **from £35,646 to £29,409.** Please note, TAG ICERs incorporates the new rates for allergic reactions (see Issue 1). If a longer time horizon is employed up to 50 years (as in the base case for the manufacturer's model) the ICER for the TAG model is £27,886 which is very similar to that of the manufacturer (£27,573 with exponential discounting and £28,402 with cyclic discounting – see originally submitted evidence and manufacturer's response to the TAG assessment report). As a result the different doses used by the TAG compared to those used by the manufacturer appears to be the main driver in the difference in the ICER estimated by the TAG of £35,646 and the manufacturers base case ICER of £27,573. In addition, when a longer time horizon is used in the TAG model, almost equivalent results are seen compared to the manufacturer's submitted model and the adaptation with cyclic discounting. This should provide further reassurance that the difference is not due to the method of discounting alone as suggested by the TAG (see Issue 4 in PharmaMar's response to the TAG Assessment Report). We strongly feel that assuming the dosing schedules from the OVA-301 study (as opposed to UK clinical practice which includes unlicensed alternatives) should be used in the base case model in order to align with the fact that clinical effectiveness and safety outcomes from the model are also based on the dosing assumptions from the OVA-301 study.			

Issue: the TAG requests clarification regarding the details and reasons for censoring within OVA-301

Description of problem	Description of proposed amendment	Justification for amendment	BMJ-TAG response
[redacted]	PharmaMar requests that the TAG acknowledges the clarification provided regarding censoring within OVA-301, and consequently it can be concluded that censoring has not unduly biased the interpretation of the results.	We expect that the suggested amendments will provide insight into the reasons for censoring, and give evidence that the survival results of the OVA-301 study are robust.	Comment noted, no change required

[redacted]			

[redacted]

Table 10. Reasons of censoring (progression-free survival) in OVA-301.

Reason	Treatment arm				Total	
	PLD		Trabectedin + PLD			
	n	%	n	%	n	%
Censored on the last evaluation before subsequent therapy	88	71.5	90	67.7	178	69.5
Censored on the last tumour assessment without progression (still under evaluation, progression by IA and no further evaluations, lost to follow-up, etc)	19	15.4	29	21.8	48	18.8
Censored at randomisation day + 1 (no tumour assessments while on treatment)	15	12.2	13	9.8	28	10.9
More than 18 weeks from the last assessment between last evaluation without PD and documentation of PD	1	0.8	1	0.8	2	0.8
Total	123	100.0	133	100.0	256	100.0

IA, Investigator assessment; PD, progressive disease; PLD, pegylated liposomal doxorubicin.

[redacted] The TAG also points out the same issues related to the OS analysis: *"In addition, limited details around censoring within the OS analysis have been presented within the MS. The manufacturer reports that a total of 114 patients were censored in the final OS analysis for platinum sensitive patients (approximately 27%); however, it is unclear for what reasons, and in which arm these patients were when censored." (pg 253)* *"As a result of the high degree of censoring, and the lack of information provided around the reasons for censoring, the TAG notes that censoring within this analysis may be informative. The TAG notes that the presence of informative censoring may reduce the validity of the Kaplan Meier data presented and used within the model. The TAG does note, however, that censoring is ******** (in terms of both number of patients and proportion of patients) between the two arms of the study on aggregate, although it is unclear at what time points censoring occurred." (pg 254)* Based on this comment, PharmaMar has conducted an additional analysis to demonstrate the breakdown of the OS for the platinum sensitive patients [redacted]			

[redacted]	[redacted]		[redacted]		[redacted]				
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			

Issue: the TAG notes that the assessment of a statistical significant difference in PFI was estimated based on the full population (i.e. including platinum resistant/refractory patients) rather than for platinum sensitive patients alone

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>BMJ-TAG response</th></tr>
<tr>
<td>
In the Assessment Report consultation “the TAG notes that the assessment of a statistical significant difference in PFI was estimated based on the full population (i.e. including platinum resistant/refractory patients) rather than for platinum sensitive patients alone.” (pg 253)

On page 18 of the manufacturer’s submission, the statistical difference is reported for both the full population and the platinum sensitive population through the p value.

That is:
<table>
<tr><th></th><th>Trabectedin plus PLDH</th><th>PLDH monotherapy</th><th>P value</th></tr>
<tr><td>Mean PFI (all patients within OVA-301)</td><td>10.6 months</td><td>13.3 months</td><td>P = 0.009</td></tr>
<tr><td>Mean PFI (platinum sensitive patients within OVA-301)</td><td>14.3 months</td><td>19.0 months</td><td>P = 0.002</td></tr>
</table>
</td>
<td>PharmaMar requests that the TAG acknowledge that statistical significant difference in PFI was provided for both the full population and the platinum sensitive patients alone.</td>
<td>To ensure the TAG and AC have all available information to inform decision making.</td>
<td>The TAG thanks the manufacturer for the clarification, and apologises for this omission in the Assessment Report. This has been corrected in the latest version of the report.</td>
</tr>
</table>

Issue: the TAG requests clarification regarding the derivation of HRQoL

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>BMJ-TAG response</th></tr>
<tr><td>The TAG requested clarification around the derivation of HRQoL from OVA-301:

“Although not reported, the TAG considers it likely that the estimates of HRQoL were derived from the full population included within the OVA-301 trial; i.e. both platinum-sensitive patients and platinum resistant patients.” (pg 255)

The mean utilities used in the stable and progressive states were 0.718 and 0.649, respectively [ScHARR 2010]. These were used following the recommendation from the ERG during the original STA: “the ERG believes that the most sensible health state utility values are those originally presented in the MS, i.e. health state utilities estimated for the combined treatment group across all platinum-sensitive women (Table 28)” [ScHARR 2010].

Table 28: Health state utilities used in the original MS (reproduction of table 36, p 141 in the MS)
<table><tr><th></th><th>Mean</th><th>Std Error</th><th>Lower 95% CI for Mean</th><th>Upper 95% CI for Mean</th></tr><tr><td>Stable</td><td>0.718</td><td>0.01</td><td>0.699</td><td>0.737</td></tr><tr><td>Progressive</td><td>0.649</td><td>0.019</td><td>0.611</td><td>0.686</td></tr></table>
As described above these utilities were derived for the combined treatment group across all platinum sensitive women (PFI > 6 months) within the OVA-301 trial. This does not include platinum resistant women.</td>
<td>PharmaMar requests that the TAG acknowledges the clarification provided on the derivation of HRQoL.</td>
<td>To ensure the TAG and AC have all available information to inform decision making.</td>
<td>Comment noted, no change required</td></tr>
</table>

Issue: the TAG suggests that the discounting methodology overestimates the QALY gain in the manufacturer's model

Description of problem	Description of proposed amendment	Justification for amendment	BMJ-TAG response
PharmaMar would like to emphasise that the model structure presented as part of the manufacturer's submitted evidence was based solely on the structure created by a NICE TAG during TA91. Cost-effectiveness estimates from this model structure have been shown to be robust enough to inform NICE recommendations for therapies within relapsed ovarian cancer during TA91. We therefore challenge that by suggesting the submitted model structure and discounting methodology do not provide plausible estimates of cost-effectiveness, there is inconsistency between what is deemed acceptable in TA91 and the review in progress. We acknowledge the criticism by the ERG involved in TA222 which has been noted by the BMJ-TAG: *"Discounting cannot be easily implemented in such a model structure. Ideally a state transition-type Markov trace element should be constructed to facilitate the implementation of discounting." (pg 363)* Although this highlights that it is more challenging to implement discounting in such a model compared to standard cyclic discounting in a Markov trace, we would point out that this critique does not suggest discounting is incorrect or inappropriate when implemented within the model structure. Nor does it suggest that QALY gains are overestimated by such a method, which has been extrapolated by the TAG. Furthermore, we would highlight that we used the "corrected approach" for discounting recommended by the ERG (Sheffield University) during TA222	PharmaMar request that the TAG amend the report to state that the discounting method does not overestimate the QALY gain in the manufacturer's model, and that by using the exponential or cyclic methods of discounting similar results are observed.	The interpretation that QALYs gained is overestimated by the manufacturer's model is unfounded. Considering the Excel example (Appendix 1) and updated cost-effectiveness model (Appendix 2) similar results are observed.	The TAG thanks the manufacturer for their comments and for the additional analyses provided (Appendix 1 and 2). In summary, the manufacturer asserts that: 1. Criticism of the discounting methodology used in TA91 represents inconsistency in what is deemed acceptable. 2. The method of discounting used in the PharmaMar model does not overestimate the QALY gain. The manufacturer's rationale for this assertion is as follows: a. If QALY gain is overestimated by discounting then costs will also be overestimated; b. The TAG's approach to drug cost calculation (Issue 2) is responsible for the difference in ICERs; c. Manufacturer sensitivity analysis using a monthly cyclic Markov approach with the discounting method used in TAG analysis estimated an ICER similar to that estimated in the manufacturer's original analysis (with PAS: £28,402 vs £27,573). **1. Inconsistent approaches between technology appraisals** The TAG considers it important to note that the TAG responsible for generating the evidence considered as part of TA91 did not have access to the same methods for

[Papaioannou et al. 2011]. As a consequence of the TAGs preference to facilitate the implementation of discounting using monthly cycles, the manufacturer's discounting method using the exponential distribution with an instantaneous rate of 3.44% was criticised: *"The TAG economic analysis did not rely upon mean estimates of PFS or OS. Instead, costs and QALYs were estimated monthly for each health state; these costs and QALYs were then discounted depending upon the year in which they fell.* *The TAG considers that, as a result of the discounting methodology used, the manufacturer may have overestimated the QALY gain. This is because, application of discounting to average estimates is unlikely to be as accurate as discounting based on monthly estimates, as the granularity of patient proportions, by health state, over time, is not captured." (pg 363)* We challenge the idea that discounting overestimated the QALY gain, and that the TAG's method is more accurate: • Firstly, if QALY gain is overestimated then one would equally expect costs to be overestimated as well since the model uses the same method of discounting for both costs and QALYs. However, the TAG suggests that *"The difference in ICER estimated between the TAG model and the manufacturer's model was a result of a difference in estimated incremental QALYs, rather than the difference in incremental costs." (pg 33)* This appears to give an inconsistent message that the discounting methodology only affects the QALYs. • Secondly, we would argue that the exponential			approximating individual patient level data used in the BMJ-TAG's economic model. Therefore, it was necessary for the TAG generating evidence for consideration in TA91 to use a model constructed around mean estimates, which in turn necessitated the use of the discounting methodology employed by PharmaMar. **2. The accuracy of discounting in PharmaMar's model** The TAG considers it important to note that the key difference in estimated ICERs between the PharmaMar analysis and the TAG sensitivity analysis (in which the same effectiveness data were used) was a difference in QALYs; 0.49 QALYs (PharmaMar) versus 0.38 QALYs (TAG). Given that the analyses carried out by the manufacturer and the TAG both used the same PFS and OS data, and the same utility data, the TAG was surprised that it was QALYs, and not costs, that were driving the difference. The TAG considers that the key remaining difference between the TAG and the manufacturer model is the method of discounting. An additional difference in the two analyses is the time horizon; the time horizon is explicitly stated in the TAG analysis as 15 years. a. The manufacturer notes that "if QALY gain is overestimated then one would equally expect costs to be overestimated as well". The TAG notes that the largest costs are experienced upfront (e.g., treatment, and administration) and therefore are likely to be less affected by discounting. b. The manufacturer also claims that the method of drug cost calculation used by the TAG is responsible for the differences in the ICER. However, the TAG notes that a difference in cost cannot impact upon the QALY estimate. In addition, as described above, the TAG does not consider that dose and cost of trabectedin

method actually provides (slightly) more accurate results since costs and QALYs over time are discounted continuously as opposed to monthly intervals with half-cycle correction. One would expect the "granularity of patient proportions, by health state, over time" to be more accurate with continuous time than partitioned cycles.
• Thirdly, we provide a simple example in Excel (Appendix 1) to show that discounting costs and QALYs continuously by the exponential method with an instantaneous rate of 3.44% should give no noticeable differences compared to cyclic discounting at 3.5% per annum. Although, the cyclic discounting method appears to produce marginally lower costs and QALYs.
• Finally, to prove the method of discounting in the model and use of mean time in state does not significantly impact results compared to a monthly cyclic Markov model, we provide an updated cost-effectiveness analysis (Appendix 2). The amends to the model include:
  ○ The addition of a 'Monthly Cycles' sheet which calculates discounted costs and QALYs each month over a lifetime horizon (50 years) at a 3.5% rate p.a.
  ○ In particular, for each health state the proportion of patients, costs and QALYs are calculated each month for trabectedin plus PLDH and PLDH monotherapy.
  ○ This analysis results in a £28,402 ICER with PAS which is a small increase compared to the £27,573 ICER with PAS submitted in the manufacturer's submission (shown on the 'Analysis' sheet in Appendix 2). Incremental costs
			plus PLDH has been overestimated.
			c. The manufacturer carried out a sensitivity analysis of their originally submitted model, which incorporated a monthly cyclic Markov approach and used the discounting methodology employed within the TAG's model. The ICER estimated by the manufacturer's sensitivity analysis was £28,402 per QALY. The manufacturer asserts that this analysis demonstrates that the "the difference in ICER estimated by the TAG, £35,646 and the manufacturers ICER of £27,573 cannot be due to the method of discounting alone".
			However, the TAG notes that under a 15-year time horizon (as in the TAG model), the incremental QALYs estimated in the manufacturer's sensitivity analysis are identical to the incremental QALYs estimated in the TAG sensitivity analysis (i.e., 0.38 QALYs). Moreover, the TAG notes that the incremental cost estimated by the manufacturer has fallen from £13,397 in the original model to £11,329 in the sensitivity analysis.
			The TAG notes that the difference in incremental costs between the manufacturer's original and sensitivity analyses is a result of a fall in the estimated cost of trabectedin plus PLDH; from £21,734 in the original manufacturer analysis to £16,844 in the sensitivity analysis. Furthermore, the TAG notes that this reduction in the cost of trabectedin plus PLDH is a result of the use of mean dose to calculate the drug costs per cycle. As discussed above, use of mean rather than intended drug dose to calculate drug costs underestimates the cost of treatment.
			Therefore, the TAG maintains that the difference between the ICERs estimated by the manufacturer's original analysis and the TAG sensitivity analysis is a result of the difference in incremental QALYs and that this difference is in turn a result, in part, of the different approaches to discounting. The TAG considers that discounting at each cycle is likely to be more accurate than estimating

and QALYs slightly reduced when considering cyclic discounting (£11,681 and 0.41) compared to the originally submitted model (£13,397 and 0.49). This aligns with the observations in Appendix 1. As discussed, although the ICER produced by cyclic discounting may be slightly more imprecise, it does not appear to largely affect the final ICER. ○ As a result the difference in ICER estimated by the TAG, £35,646 and the manufacturers ICER of £27,573 cannot be due to the method of discounting alone as the TAG suggests : *"The ICER estimated by the TAG in this exploratory analysis was £35,646 per additional QALY. This figure compares with the manufacturer estimate of £27,573 for the same comparison. The difference in ICER estimated between the TAG model and the manufacturer's model was a result of a difference in estimated incremental QALYs, rather than the difference in incremental costs. The TAG believes that this may be due to the manufacturer's method of discounting future costs and benefits;" (pg 33)* ○ Indeed, **the most likely reason for the difference is explained under Issue 2** within PharmaMar's comments on the executable model.			discounting using an exponential distribution.

Issue: importance of adjustment of PFS and OS data using PFI as a continuous variable and interpretation of cost-effectiveness results

Description of problem	Description of proposed amendment	Justification for amendment	BMJ-TAG response
As discussed in the manufacturer's submission, adjusting PFS and OS data for potential covariates was explored. This analysis found a noticeable difference between treatment arms including a 4.7 month (25%, p=0.002) difference in PFI. As a result PFS and OS data were adjusted by covariates including PFI. A scenario analysis was conducted to identify the impact of not adjusting for PFI and results proved to be very sensitive with significantly worse fitting survival distributions. For the base case, the TAG does not adjust for imbalances observed in the PLDH arm, which is acknowledged as an important driver of results: *"However, the TAG considers that the difference in the ICER between the TAG's and manufacturer's base case analyses is predominantly a consequence of the use of adjusted clinical effectiveness data; adjusted for baseline characteristics such as PFI (as a continuous variable). The TAG notes that adjustment of clinical effectiveness data for key prognostic factors such as PFI is likely to result in more accurate estimates of PFS and OS." (pg 363)* We are pleased that the TAG have acknowledged this weakness throughout the Assessment Report, and that the scenario analysis which does adjust for these imbalances is considered to be the most accurate cost-effectiveness estimate for trabectedin plus PLDH vs. PLDH monotherapy: *"The TAG considers that the ICER estimated in the*	PharmaMar request that the TAG clarify which cost-effectiveness estimates should be used to inform cost-effectiveness decisions for trabectedin plus PLDH vs. PLDH monotherapy. Although the non-adjusted ICERs provide a comparable dataset, following the discovery that PLDH is the most cost-effective treatment under this assumption, the adjusted ICER of trabectedin plus PLDH vs. PLDH monotherapy is more appropriate and should be used to inform cost-effectiveness decisions.	It is unclear whether adjusted or unadjusted cost-effectiveness for trabectedin plus PLDH vs. PLDH monotherapy should be used to inform cost-effectiveness decisions.	The TAG is grateful to the manufacturer for their comments and agrees that additional clarity may be of use to the Appraisal Committee. The TAG presents base-case results for two platinum-sensitive networks (platinum-based therapies, and non-platinum-based therapies) and one platinum-resistant/refractory network. These results are subject to a number of sensitivity analyses including probabilistic analysis, scenario analyses and one-way sensitivity analysis. As pointed out by the manufacturer, one of the scenario analyses carried out for platinum-sensitive network 2 included use of the manufacturer's head-to-head data for PFS and OS, which had been adjusted for baseline characteristics. This is a sensitivity analysis and not a base case analysis, and should be interpreted as such. As the TAG notes throughout the Assessment Report, the ICER obtained from this analysis cannot be compared with ICERs obtained from the base case analyses. This is because the impact of using adjusted PFS and OS data on the cost-effectiveness of trabectedin plus PLDH versus other comparators of interest is unknown. In addition, the scenario has not been subject to any additional testing, such as probabilistic analysis. However, the TAG does consider the ICER obtained from TAG sensitivity analysis to be the most accurate representation of the cost-effectiveness of trabectedin plus PLDH versus PLDH monotherapy.

TAG's scenario analysis is likely to be the most accurate reflection of the cost-effectiveness of trabectedin plus PLDH versus PLDH" (pg 363) However, we feel that there is some confusion as to which ICER the TAG believe is more appropriate to evaluate the cost-effectiveness of trabectedin plus PLDH vs. PLDH and other non platinum agents. The TAG state that: *"However, as efficacy data used in the TAG's base case model was unadjusted (to provide a consistent dataset), the TAG notes that the head-to-head ICER generated from using adjusted efficacy data is not comparable with ICERs estimated for other treatments in the TAG's base case analyses." (pg 30)* *"The TAG notes that, given the data available, it is not possible to adjust survival for the remaining treatments in the network in a similar way, and therefore the results of the scenario analysis should be considered independently." (pg 35)* These statements seem at odds with the interpretation that the scenario analysis offers the most accurate reflection of cost-effectiveness for trabectedin plus PLDH vs. PLDH monotherapy. We acknowledge that whilst the probabilistic ICER for trabectedin vs. PLDH without adjusting for covariates (£81,353) is considered more consistent and comparable with other non platinums, it is significantly inaccurate compared to the ICER calculated in the scenario analysis (£35,646). We would therefore recommend to the ERG a two stage approach: 1. Firstly, a consistent approach is applied to all non platinums by not adjusting for covariates. 2. Secondly, following the discovery that PLDH is			

indeed the most cost-effective of the non platinums, the scenario analysis should be considered to provide the most accurate reflection of the cost-effectiveness of trabectedin plus PLDH vs. PLDH monotherapy. 3. Hence, recommendations may be made with regards to the cost-effectiveness of non platinums when not adjusting for covariates, and the cost-effectiveness of non platinums when correctly adjusting for covariates. In this regard, the ICER of trabectedin plus PLDH vs. PLDH monotherapy, when covariates have been adjusted for, is the ICER for which decision makers should be basing cost-effectiveness decisions on.			

Issue: the TAG requests justification of curve fitting separately by treatment arm

Description of problem	Description of proposed amendment	Justification for amendment	BMJ-TAG response
The TAG indicated that no justification was provided for fitting parametric distributions to the Kaplan Meier data by treatment arm compared to selecting treatment as a covariate: *"These curves were fitted separately by treatment arm; i.e. treatment was not included as a covariate; the manufacturer did not provide a rationale within the submission for this methodology."* (pg 27) PharmaMar acknowledge that the rationale for this selection could have been clearer. It is important to note that all statistical analyses with regards to PFS and OS were conducted in line with the methodology recommended by the ERG of TA222 (Sheffield University): [Papaioannou et al. 2011] "Distributions were fitted to each treatment separately and adjusting for potential covariates" [Papaioannou et al. 2011] The ERG during TA222 agrees with the TAG in that the proportional hazards assumption "may not be the case in real life" [Papaioannou et al. 2011]. In addition, when considering the cumulative log hazards associated with Kaplan Meier PFS and OS (Appendix 10 of the TAG Assessment Report), it is clear that hazards are not proportional and thus fitting treatment as a covariate to the parametric curves would inappropriately assume proportional hazards. This limitation is discussed in great length within the TAG Assessment Report. Additionally, the DSU TSD provides further justification as to why curves should be fitted by treatment arm and not using treatment as covariate (assuming proportional hazards): [NICE DSU 2013] • Inspection of the cumulative log hazards suggests the proportional hazards assumption does not hold. • Proportional hazards cannot be assumed for the log-logistic parametric distribution, which has been shown to be a significantly better fit to the OS Kaplan Meier data for trabectedin plus PLDH and PLDH monotherapy based on AIC/BIC (see Appendix 7 of manufacturer's submitted evidence). Hence less accurate models for OS would have to be selected.	PharmaMar request that the TAG acknowledge that following consultation, the manufacturer has provided a clear rationale for choosing to fit curves separately by treatment arm, which mitigates the bias of assuming proportional hazards and provides more reflective estimates of PFS and OS.	To ensure the TAG and AC have all available information to inform decision making.	Comment noted, no change required

• "If the proportional hazards assumption does not seem appropriate it is likely to be most sensible to fit separate parametric models of the same type" [NICE DSU 2013]. This is exactly what we did for both PFS and OS. We are pleased that the TAG have acknowledged that the manufacturer's statistical analysis used during the TAG's scenario analysis provides the most accurate cost-effectiveness estimate for trabectedin plus PLDH vs. PLDH monotherapy: *"The TAG considers that the ICER estimated in the TAG's scenario analysis is likely to be the most accurate reflection of the cost-effectiveness of trabectedin plus PLDH versus PLDH" (pg 363)*			

Target ovarian cancer comments

Issue: technical content

Description of problem	BMJ-TAG comment
1) Pegylated Liposomal Doxorubicin Hydrochloride (Caelyx) We hope that there is capacity to deliver the required volume of PLDH to women who are suitable to receive it as a treatment option. Supplies of PLDH were severely disrupted at the end of 2011 and initially were not expected to resume till 2014. However production began again late last year, but we are not clear whether supplies are at capacity. 2) The number of women diagnosed with staged disease On pg 41 it is stated that 60% of women are diagnosed with stage III or IV disease. This data is from the Eastern Cancer Region and depicts that almost all women are staged. From the International Cancer Benchmarking Partnership study (Maringe et al, 2012), the UK presents quite differently. The data collected includes that of the Eastern Cancer region, but also includes UK data in addition to other international data and highlights that the proportions of unstaged tumours range from 4% (Norway) to 32% (UK). We would hope that the data from the International Cancer Benchmarking Study is used to ensure there are no misassumptions on the cost of treatments.	1) The BMJ-TAG thanks Target Ovarian Cancer for raising this important point. 2) The TAG thanks Target Ovarian Cancer for flagging this source of information. The TAG considers it important to note that this incidence figure was not utilised by the TAG in a budget impact analysis.

Issue: general

<table>
<tr><th>Description of problem</th><th>BMJ-TAG response</th></tr>
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1) Title of the assessment report

The title does not state that the focus is of women who have received prior platinum-based treatment

2) Categorisation of platinum sensitivity

We noticed that at times in the document partial platinum-sensitive and fully platinum-sensitive were referred to as platinum-sensitive. It is important that the document is specific as to whether they are referring to partially platinum sensitive or fully platinum sensitive. Also we recommend that it is acknowledged early on in the document that some women are allergic to platinum in the first place.

3) Platinum allergic patients were not analysed separately (pg 15)

We understand that platinum allergic patients were considered by the TAG, we also hope that the TAG consulted with clinical experts to come to the assumption that treatments for platinum allergic patients would respond in the same manner to other treatments.

4) The approach

As far as we can determine, we regard the approach taken to develop 2 networks for platinum sensitive treatments as appropriate, and agree with the assumptions made, and most importantly with the need to acknowledge that for those women who are still platinum sensitive, some of them will not be able to tolerate further platinum treatment due to toxicity.

5) Overall survival and progression free survival

We welcome that the TAG consider both overall survival and progression free survival, as progression free survival vital for women as it is time without the cancer returning when women

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1) The title of the report was taken from the final scope for this MTA

2) The definition of platinum-sensitive disease used within the Assessment Report encompasses the two separate patient groups of partially platinum-sensitive disease and fully platinum-sensitive disease (see extract below taken from Table 13 page 44 of the Assessment Report).

Table 13. Categorisations of platinum sensitivity used in choice of second and subsequent lines of treatment of ovarian cancer

<table>
<tr><th>Categorisation</th><th>Definition</th></tr>
<tr><td>Platinum sensitive</td><td>Disease that responds to first-line platinum-based therapy but relapses 6 months or more after completion of initial platinum-based chemotherapy</td></tr>
<tr><td>Partially platinum-sensitive</td><td>Relapses between 6 and 12 months after completion of initial platinum-based chemotherapy</td></tr>
<tr><td>Fully platinum-sensitive</td><td>Relapses 12 months or more after completion of initial platinum-based chemotherapy</td></tr>
<tr><td>Platinum resistant</td><td>Disease that relapses within 6 months of completion of initial platinum-based chemotherapy</td></tr>
<tr><td>Platinum refractory</td><td>Disease that does not respond to initial platinum-based chemotherapy</td></tr>
</table>

3) The TAG thanks Target Ovarian Cancer for their comment; the TAG consulted with clinical experts who provided support for this assumption. See below extract taken from p268-p269 of the Assessment Report

“Additionally, the TAG sought clinical advice around expected response to treatment for patients with an allergy to platinum-based compounds compared to those without an allergy. It was noted by clinical experts that response to non-platinum based therapies would be expected to be consistent between patients with or without an allergy or

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</table>

can live their lives as fully as they can.	intolerance to platinum based therapy. The TAG therefore considers it appropriate to include platinum allergic patients in the platinum sensitive and platinum refractory subgroups. Therefore, a separate analysis of platinum allergic patients has not been carried out; however, treatment options for platinum allergic patients are assumed to exclude platinum-based therapies." 4) The TAG is grateful for Target Ovarian Cancer comments on the approach 5) The TAG thanks Target Ovarian Cancer for their comments on the importance of progression-free survival for women with ovarian cancer

Issue: suggested research

Description of problem	BMJ-TAG response
1) Suggestion for RCT to establish link between platinum sensitive network 1 and platinum sensitive network 2 We believe that conducting this research could limit women being involved in other trials of new treatments, and we are not clear this type of trials would be good use of resources. 2) Best supportive care We support future research on best supportive care as no one has quantified this yet. Knowledge of this would help decide what best supportive care looks like for clinicians. Due to the importance of this, we are funding the UK arm of an international prospective study investigating the clinical benefits of palliative treatments and also to establish how treatments affect quality of life.	1) The TAG thanks Target Ovarian Cancer for their comment on the suggested research. The TAG acknowledges that research establishing a link between platinum-sensitive network 1 and platinum-sensitive network 2 would be useful only if this was thought to be important by the wider clinical community. The TAG notes that, after review of clinical trial registries, two RCTs are currently ongoing in partially platinum-sensitive patients (PFI 6–12 months) in which platinum-based therapies are compared with non-platinum based therapies. These trials may provide sufficient comparative information for the wider clinical community. 2) The TAG considers that research into best supportive care and quality of life is of importance, and thanks Target Ovarian Cancer for flagging this research.

GSK comment

Description of problem	BMJ-TAG response
We have only one comment, which is to clarify the licensed indication for topotecan. The assessment report specifies on page	The BMJ-TAG thanks GSK for highlighting this error. The text on page 13 has been amended in line with the text on pages 45 and 46 of the Assessment Report.

13 that the licence is after failure on 1st line platinum-based therapy: Paclitaxel (various manufacturers) is licensed for first-line treatment of ovarian cancer in combination with platinum-based chemotherapy, and as second-line treatment of ovarian cancer after failure of standard platinum-based therapy. PLDH (Caelyx®, Jansen-Cilag) and topotecan (various manufacturers) are licensed for the treatment of advanced ovarian cancer after failure of first-line platinum-based therapy. Please note that there is no specification that 1st line therapy should be platinum-based in the licensed indication, which is: Topotecan monotherapy is indicated for the treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy.	