Pierre Fabre Response to Clarification Requests

Section A: Clarification on effectiveness data

A1. (Page 21: Table A3, decision problem). Please explain asterisk in outcomes box.

Response: Study 302 is the only randomised study at this stage of treatment and there is no comparable response rate data. The implications for patients entering studies that randomised against BSC tend to recruit patients that are closer to the end of life, with relatively high tumour burden and relatively short expected survival, as discussed in 2.6 (page 17). In these circumstances, when we have been commissioned to respond to a scope that includes "Response rates", we sometimes draw on results from published phases II studies, even if it is only to set an expectation. This would be unfair as patients entered into cancer phase II studies tend to be much fitter than those willing to be randomised to BSC, with a smaller tumour burden and an objective response (and longer survival) is more likely. An apparent response rate of 29% (gemcitabine) in a phase II would normally be expected to prompt urgent development of the indication but clearly did not (see page 111 point (3)). This asterisk was to remind us to explain why we had not compared response rates. Clearly we forgot, so thank you for this opportunity for a supplementary response.

A2. (Page 24). Please explain why non-inferiority trials were explicitly stated as an exclusion criterion whereas equivalence trials were not.

Response: The term non-inferiority was used to generically describe trials that were designed to reject the possibility that differences in treatment effects equal or exceed preset limits and therefore included both non-inferiority and equivalence trials. In retrospect it would have been better to use both terms in the Table on page 24.

A3. (Page 25). Please supply a list of the 77 excluded references grouped by reason for exclusion, plus any other excluded references that relate to second line therapy.

Response: These references are in the appendix accompanying this response, grouped under reasons for exclusion headings. Appendix of excluded papers). They are summarised by; numbers of papers in each excluded group, the titles and citations of the papers in each group and citations with abstracts of the papers in each group.

A4. (Page 30: Table B6) Was the difference in performance status between the VFL+BSC arm and the control arm statistically significant?

Response: The difference in performance status between the Vinflunine+BSC arm and the control arm was not statistically significant (p=0.071)

A5. (Page 30: Table B6). Were the differences in prior cisplatin therapy and prior carboplatin therapy between the vinflunine plus BSC arm and the control arm statistically significant?

Response: The difference in prior cisplatin/carboplatin therapies between the vinflunine plus BSC arm and the control arm was globally not statistically significant (p=0.114).

- The difference in prior cisplatin therapy between the vinflunine plus BSC arm and the control arm was not statistically significant (p=0.153) while the difference in prior carboplatin therapy between the vinflunine plus BSC arm and the control arm was statistically significant (p=0.044).

A6. (Page 30: Table B6). Please clarify sample size for prior CTx.

Response: The number of patients with data does not match the total for each group because the dates of relapse or progression after first line were missing for patients who did not receive a first line chemotherapy for advanced disease, or non applicable for three patients in the control arm who have never progressed after the first line chemotherapy.

A7. (Page 31). Response rates are listed as secondary outcomes. This appears inconsistent with an earlier statement in the manufacturer submission (MS; p. 21) that there would be no comparative data for response rates in this end of life population with a heavy tumour burden. Please clarify.

Response: See response to A1 above.

A8. (Page 31). Quality of life and clinical benefit are included as outcomes but are not classified either as primary or secondary outcomes – instead they are referred to as “other criteria”. What does this mean and how does it influence their analysis and interpretation?

Response: According to the protocol (section 2.2), Quality of life and clinical benefit are considered as secondary outcomes.

A9. (Page 31-32). Please clarify the relationship between the independent review committee (IRC), independent review panel (IRP), independent response review panel (IRRC) and Synarc. It is stated later in the MS that the IRC was

blinded to the intervention received. Does this blinding apply to IRP, and IRRC and Synarc?

Response: The independent review panel (IRP) was consulted to review tumour assessments of data for investigator-identified responders and patients with long duration of stable disease in the vinflunine plus BSC arm only; as per the original charter this review was not blinded.

A second independent, blinded review (IRC) of all tumour assessments for all patients in both arms was scheduled at the end of study in order to better substantiate the response rate and progression free survival and ensure the comparability of both arms in respect of these items. For this purpose Synarc Inc. a contract Research Organisation (CRO), was committed to perform this blinded independent review.

The Independent Response Review Committee (IRRC) only pertains to one of the phase II studies (Vaughn et al Cancer 2009;115:4110-7) and was the body that reviewed all tumour assessments and the duration of response or stable disease.

A10. (Page 32). Please explain the rationale for the superiority hypothesis. Only two publications referred to on page 32 (von der Maase 2000; Sternberg 1988) and two different publications are referred to on page 38 (Culine et al. 2006; von der Maase et al. 2006 – the latter not in the reference list).

Response: When the protocol was written, there was still no standard salvage therapy for patients with advanced or metastatic transitional cell carcinoma of the urothelial tract (TCCU) whose disease has progressed after or during a prior platinum-containing regimen. These patients have a poor prognosis and a median survival rarely exceeded 3 to 6 months (von der Maase 2000; Sternberg 1988).

The analysis of data from the first Phase II study (L 00070 IN202 P1) of VFL as second-line therapy conducted in Europe, showed that overall survival (OS) was 6.6 [4.8-7.6] months respectively (Culine et al, 2006). This observation suggested that vinflunine might improve survival for patients with TCCU who had been previously treated with platinum-containing regimens.

Based on these publications, the target population in the protocol and the discussion with some medical key leaders, a phase III study was performed to demonstrate the superiority of vinflunine plus BSC over BSC in terms of overall survival on the basis of statistical hypothesis that the median survival in the vinflunine plus BSC group would be 6 months (Culine et al, 2006) versus a median survival of 4 months in BSC group (von der Maase 2000; Sternberg 1988).

Please replace the reference “von der Masse 2006” by “von der Masse 2000”

A11. (Page 32). Please clarify the meaning of the bullet point stating “A follow up time of 6 months after randomisation of the last topic”.

Response: The correct sentence is: A follow up time of 6 months after randomisation of the last patient.

A12. (Pages 32-33). The MS reports that data were censored at the start date of further chemotherapy or the date of last news but it is unclear what this means. Please provide further explanation of the method of censoring used and the implications of these censored data when interpreting the statistical analyses.

Response: Overall survival is defined as the duration between the date of randomisation and the date of death due to any cause. For those patients lost to follow up or who have not died when the target OS event goal is reached, survival duration was censored at the date of last news (i.e. : date of last administration, tumour assessment, clinical examination, ECG, neurological examination, audiogram examination, haematological or biochemistry assessment or date of last contact).

In order to determine the role of the study treatments arms in survival, an additional supportive analysis was done with the overall survival time censored at the time of the first further chemotherapy. For patients who received secondary chemotherapy, survival duration was censored at the start date of the further chemotherapy. For patients who did not receive any further chemotherapy but were lost to follow-up or did not have a record of death, the survival duration was censored at the date of last news.

A13. (Page 33). The MS refers to prognostic factors including “the presence of lymph nodes”. Please clarify whether this means the involvement of lymph nodes/presence of metastases rather than just presence of lymph nodes.

Response: This means the involvement of lymph node metastases. Lymph node metastases were identified as potential prognostic factors in first-line therapy (Bajorin et al 1999 J Clin Oncol 17:3173-81).

A14. (Page 38: Table B8). Results for vinflunine plus BSC are exactly the same for all 3 analyses (ITT, eligible ITT and per protocol) even though the groups have different numbers of patients. Please confirm if these are the correct data.

Response: We confirm that the results for vinflunine plus BSC are exactly the same for all 3 analyses (ITT, eligible ITT and per protocol) even though the groups have different numbers of patients. The correct P value and HR in the per protocol are given in the following table.

Table B8: Summary of OS results for the ITT and eligible ITT populations

Efficacy primary endpoint: overall survival				
Population	Median months (95% CI)		Stratified log rank *P* value	Hazard ratio (95% CI)
	Vinflunine+BSC	BSC		
ITT	6.9 (5.7 to 8.0)	4.6 (4.1 to 7.0)	0.2868	0.88 (0.69 to 1.12)
Eligible ITT	6.9 (5.7 to 8.0)	4.3 (3.8 to 5.4)	0.0403	0.78 (0.61 to 0.99)
Per-Protocol	6.9 (5.7 to 8.0)	4.3 (3.8 to 5.4)	0.0197	0.75 (0.59-0.96)

The above HR and P value (0.75, p=0.0197) correspond to the date of initial cut-off (November 2006) while the HR and P value in the MS (0.74, p=0.013) correspond to the update of OS on May 2007.

For more details, you can have a look at Overall Survival (OS) - Per protocol population (Page 43, EMEA report)

"*Median OS for per protocol analysis was 6.9 months in the vinflunine arm and 4.3 months in the BSC arm. The risk of death is reduced by 25% in the vinflunine + BSC arm compared to the BSC arm: HR of 0.75 (95% CI: 0.59; 0.96 p=0.0197). In a subsequent update, OS in the per protocol patient population showed a 2 months advantage favouring vinflunine + BSC (6.9 month versus 4.3 months), with a reduction of risk of death by 26% HR 0.74 (95% CI: 0.59, 0.94). This difference was statistically significant (p = 0.0130).*"

A15. (Page 39). Please provide rationale (and give reference if applicable) for the choice of prognostic factors in the planned multivariate analysis. Please also explain why the involvement of lymph nodes/presence of metastases is not included in this analysis.

Response: The choice of prognostic factors in the planned multivariate analysis was based on the publication of Bajorin et al. "Long term survival in metastatic transitional cell carcinoma and prognostic factors predicting outcome of therapy".

The presence of lymph nodes metastases was not kept as a prognostic factor in the model because it was not statistically significant (p=0.481) (Bajorin et al 1999 J Clin Oncol 17:3173-81)..

A16. (Pages 41 & 42: Table B10). Please clarify what is meant by an extended multivariate analysis and why the results for this analysis in the ITT population differ from the results for the pre-specified multivariate analysis in the same population presented table B9 (page 40).

Response: Excluding patients from the ITT analysis leads to a non-respect of the randomisation scheme from which potential biases may arise when the analysis of OS was conducted in the eligible population. Possible imbalances in the patient characteristics between the treatment groups may result from this exclusion.
So, to address these potential biases, a set of covariates for OS in TCCU patients including the pre-specified prognostic factors and additional baseline characteristics was identified: sex, age, disease stage at diagnosis, time from diagnosis to randomisation, bone, liver, visceral involvement, lymph nodes, number of organs involved, disease status at randomisation, creatinine clearance, ASAT, AKP, Hb, PS, Pelvic irradiation, refractory status.
Then, an extended multivariate Cox analysis was performed including this set of covariates to adjust the effect of the treatment arm on potential confounding factors. The aim of this analysis was to verify whether or not the VFL has still a significant impact on OS in the targeted population.
The results of this analysis could be different from those presented in table B9 because the extended multivariate analysis was adjusted on more covariates than the pre-specified multivariate analysis.

A17. (Page 43). It is not clear why results of a per protocol (PP) analysis are reported, as this is not the analysis population used to test superiority. Although PP may be used to support results from an ITT analysis no discussion of this is given. Please clarify.

Response: The per protocol (PP) population was defined in the protocol as secondary efficacy analysis but as stated by the CHMP review in the Day 150 Joint Response Assessment Report, the results of a Per-Protocol population should always be treated with caution, particularly in a randomized study with a no-treatment arm. Indeed, patients can be removed for post-treatment violations which can be related to treatment, the analysis becoming a non-randomized comparison. The PP analysis may be used just as supportive analysis.

A18. (Pages 44 & 46). Missing footnote. Please clarify whether the footnote “a” in Figures B5 and B6 refers to the stratified log rank test, as in the preceding figures.

Response. Yes. Footnotes are the same (EMEA CHMP Assessment Report)

A19. (Page 45). Please clarify why the results for disease control rate (DCR) but not for progression-free survival (PFS) are different to those reported in the primary publication (Bellmunt et al., J Clinical Oncology 2009; 27: p. 4456). DCR values in the primary publication are 41.1% and 24.8% for the two study groups whereas in the MS (p. 45) DCR values of 55.1% and 27.1% are given.

Response: The results reported in the primary publication correspond to the results in the ITT population while those reported in the MS report correspond to the results in the evaluable population for efficacy.

The DCR values are expressed in several ways in the primary publication (Table 3, p 4458) and in the EMEA report (Table 22 and Table 23, p 49-50). To simplify the manufacturers submission (p 45) we expressed DCR as partial response (8.6%) plus stable disease (8.6% + 46.5% = 55.1% for vinflunine + BSC and 27.1% for BSC) consistent with Table 3, p4458 of the primary publication under “Overall response in evaluable patients” (n=185 / 85) and used by the EMEA to summarise efficacy in Table 22 (p49) of their report.

A20. (Pages 59 & 60). The MS reports the median overall survival as 7.9 months (95% CI 6.67 to 9.69 months). However, in the primary publication (Vaughn et al., Cancer, 2009; 115: p. 4113) the corresponding data are 8.2 months (95% CI 6.8 to 9.6 months). Please explain the discrepancy.

Response: The median overall survival (OS) in the primary publication (8.2 months) corresponds to the OS update performed after the final CSR for CA183001.

Again to simplify the MS, we chose to remain consistent with the EMEA report (application submitted in Feb 2008, median overall survival = 7.9 months, p55) rather than the later final publication by Vaughn et al (2009) when, with longer follow-up, the survival had improved slightly to 8.2 months.

A21. (Pages 59 & 60). The rate of disease control, duration of disease control, response duration, and progression-free survival are not reported in the primary publication (Vaughn et al.). Please clarify the source of these data.

Response: The rate of disease control, duration of disease control, response rate and progression-free survival are reported in the Clinical Study Report (CSR) of the CA 183001 study (CA001).

A22. (Page 124). The question "Were there any unexpected imbalances in drop-outs between groups?" is answered "yes". This appears inconsistent with the text, which states there were no differences in drop out rates. Please clarify.

Response: There is no difference in the drop-out rate between groups and the question "Were there any unexpected imbalances in drop-outs between groups?" should be answered "No". This was an error in the MS.

A23. The vesicant nature of vinflunine is not mentioned in the MS. Please explain whether there would be clinical, safety or cost implications of using a vesicant.

Response: A large number of cytotoxic agents in regular, routine use are classed as vesicants (The cytotoxic Handbook 4th edition page 133). Group 1 vesicants include anthracyclines, paclitaxel and all the vinca alkaloids (including vinflunine).

Vinflunine will only be used by centres that are experienced in the routine use of cytotoxic chemotherapy and we can reasonably expect that the risk of extravasation will be minimised. The best estimate regarding the likely or potential incidence of extravasation with the whole vinca class of drug is probably the National Patients Safety Agency Rapid Response Report Supplementary information from 2008 (NPSA/2008/RRR04, page 7). There is insufficient global experience with reported incidents of extravasation with vinflunine on the safety data base (0) but the overall incidence of extravasation with whole vinca alkaloid family is estimated to be 0.027% (NPSA report above). Given this relatively low incidence and general, routine use of vesicants in cancer treatment, we did not flag this as a separate cost in the MS. Naturally, remain vigilant to patient safety.

Section B: Clarification on cost-effectiveness data

B1. (Page 69; section 6.2.1). The MS states that the population modelled consists of advanced or metastatic TCCU patients who failed a prior platinum-containing regimen. Bellmunt et al. 2009 describe the trial participants as patients with locally advanced or metastatic TCCU with documented progression after first-line platinum. Please confirm whether trial participants correspond to patients who stopped responding to a platinum-containing regimen?

Response: For the study L00070 in 302 P1, the inclusion criteria were the following:

"Patients with progressive disease who failed or progressed after first line platinum-containing chemotherapy for advanced or metastatic disease. First line chemotherapy was defined as receiving at least 2 cycles. Nevertheless, in case of clear evidence of progressive disease after the first cycle of previous chemotherapy patients were accepted and stratified as refractory patients".

So we can confirm that the eligible ITT population had stopped responding or had relapsed following platinum-containing chemotherapy. It is evident from Bellmunt et al (J Clin Oncol 2009; 27:4454-61) and the EMEA report that the 13 ineligible patients had not progressed and the EMEA considered this a legitimate reason for their exclusion.

B2. (Page 76; table B31). The hazard ratio for overall survival (OS) shown in the table is 0.70. The text states this is based on the data from study 302 for the eligible ITT patient population. However, in Figure B4 (page 40), the hazard ratio is shown as 0.78. Please confirm the actual value used in the model. If this differs from 0.78, please explain the reason for this discrepancy.

Response: In table B4 page 41 the OS results used are issued from the results of the clinical trial published in the Bellmunt article (Bellmunt et al 2009 J Clin Oncol 27:4454-61).

In page 76 table B31, we used the multivariate cox regression model which adjusted for significant prognostic factors at randomisation or baseline, including: (1) visceral involvement; (2) pelvic irradiation (3) ECOG performance status; (4) alkaline phosphatase; and (5) haemoglobin.

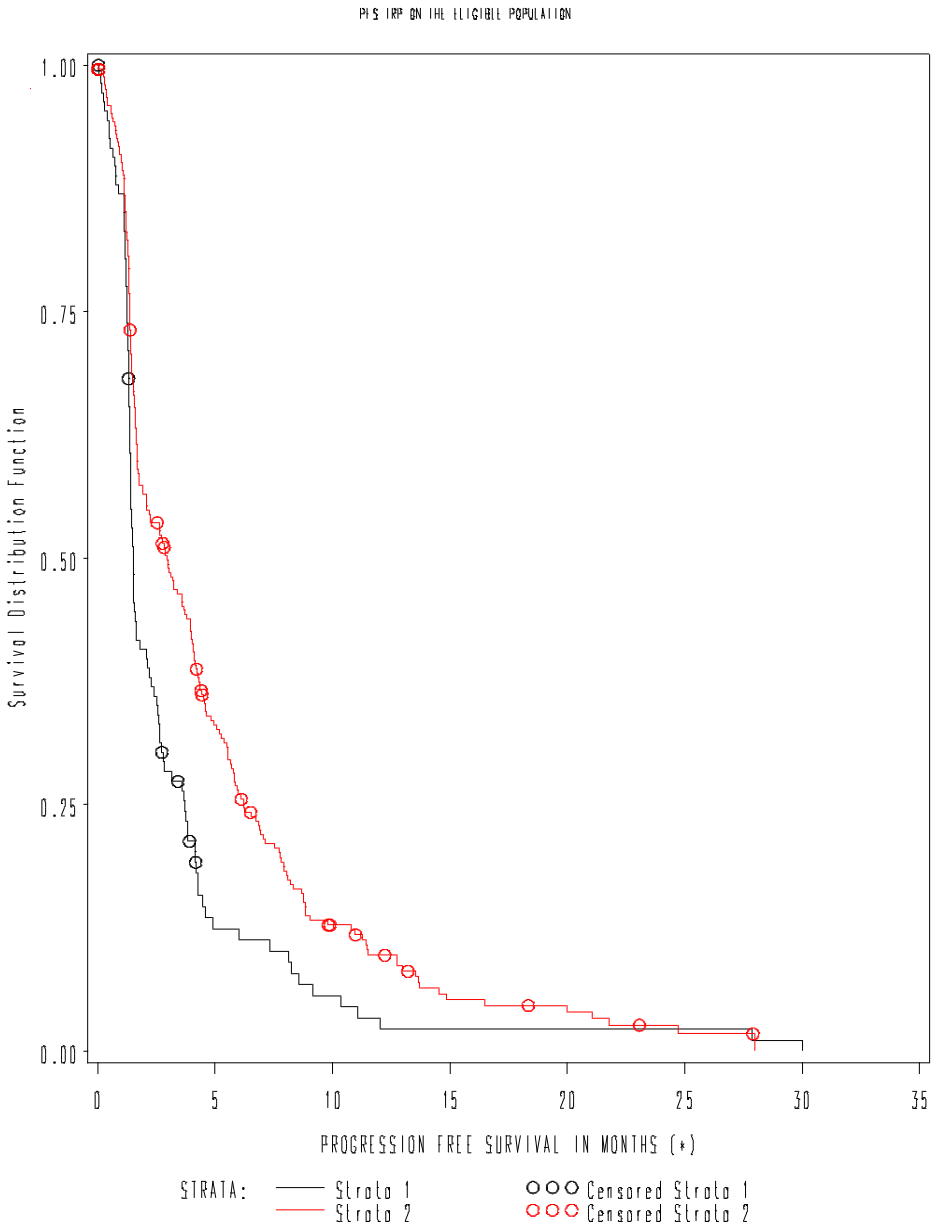
B3. (Page 76; table B31) The hazard ratio for progression-free survival (PFS) in the eligible ITT population shown in the table is 0.47. However, only the hazard ratio for the ITT population is provided in the clinical effectiveness section (Fig B6, p 46, HR 0.68). Please supply the equivalent PFS curve as that in figure B6 for the eligible ITT population.

Response: In table B6 p46 we used the PFS results issued from the clinical trial published in journal of clinical oncology (Bellmunt et al 2009 J Clin Oncol 27:4454-61)

In table B31 page 76 we used the multivariate cox regression model which adjusted for significant prognostic factors at randomisation or baseline, including: (1) visceral involvement; (2) pelvic irradiation (3) ECOG performance status; (4) alkaline phosphatase; and (5) haemoglobin

Table 1: Time related secondary endpoints in the eligible patients

	VFL + BSC	**BSC**	**p-value**
Number of patients	**249**	**108**	
PFS			
N events	225	102	
N censored	24	6	
Median (95% CI)	**3.0** (2.1-4.0)	**1.5** (1.4-2.1)	0.0003



B4. (Page 76; table B31). The mean values and standard errors for OS and PFS hazard ratios presented in this table do not match those in table B32 (p78). Please explain the reason for this discrepancy.

Response: To follow

B5. (Page 78; table B32). Please provide the source of the estimates (mean and SE) used for the risk of adverse events with vinflunine plus BSC. Please explain the differences between these values and those presented in Table B34 (page 86).

Response: To follow

B6. (Page 96; table B39). Please explain the methodology for calculating the cost for palliative radiation therapy and how the other costs shown in the table have been derived.

Response: Where available, all costs are based on the latest National Reference Costs for 2007/2008 which will be used as a basis for contract in 2009. As such, these should be regarded as 2009 costs. Where 2009 costs are not available, cost data from the nearest possible year have been reported and inflated where necessary. National Reference Costs, represent charges paid by those commissioning services (primary care trust) to those providing services (hospitals). All hospitals in England are required to report the costs of providing services. The National Reference Costs are then based on a weighted mean of costs of providing services. As such, these are expected to be provide a reasonable reflection of the cost of current care, taking into account significant variation across hospitals. The National Reference Costs form the tariff which acts as a basis for negotiation of contracts between purchasing and providing organisations. As such, these represent the actual charge that would be incurred when commissioning these services.

However, chemotherapy and radiotherapy were initially excluded from the list of case payments. Therefore discussion with clinical experts (oncologists, nurses and clinical coding specialists) have allowed to establish the appropriate codes to be used.

Finally, clinical advisors have provided information on the frequency of resource used, such as the proportion of patients who receive first line chemotherapy and the specific regimen used.

Enclosed is a detailed document on the cost used for the model.

B7. Please state when a reference for the current price of vinflunine, for example BNF / MIMS, will be available.

Response. Already available from March 2010 (PDF attached)