

## **7.09 VINFLUNINE, Concentrate solution for intravenous injection, 50 mg in 2 mL and 250 mg in 10 mL (as ditartrate), Javlor<sup>®</sup>, Pierre Fabre Medicament Australia**

### **1 Purpose of application**

- 1.1 Section 100 Efficient Funding of Chemotherapy program listing for vinflunine for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract (TCCU) after failure of a prior platinum-containing regimen. This is the third submission. The first submission was considered by PBAC in November 2011 and the second in November 2015.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Adult patients with locally advanced or metastatic transitional cell carcinoma of the urothelial tract.
Intervention	Treatment of adult patients with advanced or metastatic TCCU after failure of a prior platinum-containing regimen. A dose of 320 mg/m <sup>2</sup> , is administered via a 20 minute intravenous (IV) infusion, on day 1 of a 21-day cycle.
Comparator	Best supportive care (BSC).
Outcomes	Progression-free survival, overall survival and tolerability.
Clinical claim	The resubmission described vinflunine + BSC as superior in terms of comparative effectiveness and inferior in terms of comparative safety over BSC.

Source: Compiled during the evaluation.

## 2 Requested listing

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Price for Max. Amt		Proprietary Name and Manufacturer	
			Published	Effective		
VINFLUNINE DITARTRATE Intravenous solution 50 mg / 2 mL 250 mg / 10 mL	700 mg	4	\$ [REDACTED] \$ [REDACTED]	\$ [REDACTED] \$ [REDACTED]	Javlor	Pierre Fabre Medicament Australia
Category / Program:	Chemotherapy (Public/Private)					
PBS Indication:	Locally advanced or metastatic transitional cell carcinoma of the urothelial tract in an adult patient.					
Treatment phase:	Patient must have failed a platinum-containing regimen for this condition AND Patient must not have received neoadjuvant or adjuvant chemotherapy					
Restriction:	STREAMLINED					
Treatment criteria:	Treatment must be discontinued in patients who experience disease progression while on treatment					
Clinical criteria:	Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 1 or less.					
Prescriber Instructions	Note No increase in the maximum number of repeats may be authorised. Note No increase in the maximum quantity or number of units may be authorised. Note Special Pricing Arrangements apply.					

- 2.1 The resubmission presented a cost-effectiveness analysis and a cost-utility analysis compared with best supportive care (BSC).
- 2.2 The resubmission updated the first clinical criterion to more closely align with the TGA indication for vinflunine. It was changed from 'Patients must have disease progression following treatment with a platinum-containing regimen for advanced or metastatic disease' to 'Patient must have failed a platinum-containing regimen for this condition'. The resubmission also added the clinical criterion 'Treatment must be discontinued in patients who experience disease progression while on treatment'.
- 2.3 The restriction 'Patient must not have received neoadjuvant or adjuvant chemotherapy' remains unchanged in the current restriction. The PBAC noted in November 2015 that a large number of patients who may benefit from vinflunine will be excluded due to this restriction. The PSCR (p2) argued that this criterion is consistent with the Study 302 recruitment criteria, which excluded patients who had received adjuvant or neoadjuvant chemotherapy from enrolment.
- 2.4 The PBAC previously considered that realising the possible beneficial effects of vinflunine in clinical practice may be challenging because patient's age (likely to be older in clinical practice), any previous radiotherapy, and impaired performance status may adversely affect ability to adhere to the dose escalation protocols (PSD, November 2015, paragraph 7.5).

### 3 Background

- 3.1 TGA status: vinflunine was TGA registered on 22 February 2011 for the treatment of adult patients with advanced or metastatic TCCU after failure of a prior platinum-containing regimen.
- 3.2 Vinflunine was previously considered by PBAC in November 2011 and November 2015.

**Table 2: Summary of outstanding matters of concern**

Matters of concern	How the resubmission addressed it
<p><u>Requested price</u></p> <p>PBAC Comment: “The PBAC considered, given uncertainty of clinical benefit compared to BSC and active chemotherapy, that a lower ICER/QALY would likely result in vinflunine being considered acceptably cost-effective.” (November 2015, PSD paragraph 7.12).</p>	<p>The resubmission presented a lower incremental cost-effectiveness ratio, which incorporated a reduced price of \$█ per mg (\$█ in 2015). Effective ex-man prices: \$█ per 50 mg vial; \$█ per 250 mg vial. No risk share agreement was proposed.</p>
<p><u>Listing</u> (November 2015 PSD paragraph 7.2).</p> <p>The PBAC recalled that patients who had received neoadjuvant or adjuvant treatment were excluded from the trial (Study 302). As neoadjuvant/adjuvant chemotherapy is recommended for the treatment of localised muscle-invasive tumours, the PBAC noted that this PBS criterion would likely exclude otherwise eligible patients in clinical practice who may derive a benefit from the treatment with vinflunine.</p>	<p>The resubmission did not address this matter.</p>
<p><u>Comparator</u> (November 2015 PSD, paragraph 7.3).</p> <p>Whilst BSC is an appropriate comparator in determining the efficacy of vinflunine, it is not relevant in Australian clinical practice as vinflunine will likely replace or defer other drugs. The PBAC considered that current standard of care is preferable for the determination of relative effectiveness and therefore the translatability of the trial data to the proposed use in Australia is an area of significant uncertainty.</p>	<p>The current resubmission presented two comparators; active chemotherapy and BSC. However, the effectiveness and cost-effectiveness of active chemotherapy agents in the treatment of TCCU was not presented.</p> <p>The economic evaluation in this resubmission is based on the BSC comparison alone.</p>
<p><u>Clinical evidence</u> (November 2015 PSD, paragraph 7.5).</p> <p>The clinical evidence in the resubmission is sourced from one trial (Study 302).</p> <p>The PBAC considered that realising the possible beneficial effects of vinflunine in clinical practice may be challenging because patient’s age (likely to be older in clinical practice), any previous radiotherapy, and impaired performance status may adversely affect ability to adhere to the dose escalation protocols. In this regard, vinflunine also appears to have a narrow therapeutic window. The PBAC acknowledged that although vinflunine may have efficacy in some patients with high clinical need, the magnitude of survival gain is uncertain and at best less than 3 months, and this benefit is at the expense of significant toxicity. Therefore, the PBAC considered that there is insufficient evidence of a clinical place for vinflunine.</p> <p>The PBAC considered that the resubmission had not supported a claim of superior efficacy of vinflunine versus active chemotherapy (November 2015 PSD, paragraph 7.7).</p>	<p>The resubmission argued that the literature search for RCTs of vinflunine + BSC vs. BSC was updated. No new evidence was identified. Study 302 remains the primary RCT comparing vinflunine + BSC and BSC (N=370)</p> <p>An additional seven publications were reviewed regarding safety.</p> <p>The PSCR (p1) claimed that recent empirical studies confirmed vinflunine to be a safe and effective second line treatment in Spain [n=66 (Castellano et al, 20141)], France [n=134 (Medioni et al, 20132)] and Germany [n=77, (Retz et al, 20153)] with reported overall survival of 7.7-10.4 months – consistent with, or slightly better than, overall survival estimates in Study 302 (6.9 months). The PSCR also argued that the utility value collected from patients on vinflunine treatment in the Study 302 trial was close to 0.75 and as such does not</p>

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Matters of concern	How the resubmission addressed it
	suggest a level of toxicity or compromised quality of life to the extent that the patient would not continue to seek an extension of life.
<p><u>Analysis population</u> (November 2015 PSD, paragraph 7.6 and 7.9).</p> <p>The PBAC reiterated their view from November 2011 that whilst the eligible ITT population may be reasonable to assess the efficacy of vinflunine, the ITT population should be used in considering the effectiveness of vinflunine as the ITT population more closely approximates the likely PBS population.</p> <p>The PBAC considered that the results are highly uncertain as they are based on the eligible ITT population rather than the ITT population. In this resubmission, the PBAC noted that the use of the ITT population in a sensitivity analysis increased the cost/QALYG from \$45,000 – \$75,000 to \$75,000 – \$105,000.</p>	<p>The resubmission provided a tightened proposed restriction for vinflunine for use in patients to whom vinflunine provided the greater benefit (the mITT population).</p> <p>The resubmission acknowledged risk of leakage in many patient groups where prognosis is poor, and that benefits from alternative therapies are highly uncertain.</p> <p>The resubmission proposed using a ‘mixed’ estimate of clinical efficacy that lies between the ITT population and the mITT population (50:50) (Mean OS ITT: vinflunine + BSC=11.0, BSC=9.5; mITT: vinflunine + BSC=11.1, BSC=8.3; 50:50 ITT and mITT: vinflunine + BSC=11.1, BSC=8.9).</p>
<p><u>Utility values for progressive disease.</u> (, November 2015 PSD, paragraph 6.28).</p> <p>The post-progression utility values were pooled for the two treatment groups.</p> <p>The ESC considered pooling utility data post-progression may not be appropriate, and in this case bias the results in favour of vinflunine. Treatment-specific utility weights increased the ICER to \$45,000 – \$75,000/QALYG.</p>	<p>The resubmission justified this on the basis of the mean change in EORTC QLQ-C30 scores from baseline not being statistically significant across the two treatment groups, and the relatively low number of patients with post-progression evaluable observations.</p> <p>The resubmission argued that lower post-progression utility values in patients treated with vinflunine is almost certainly an artefact of the small patient numbers with evaluable data in each study arm. The difference between vinflunine and BSC post-progression was not statistically significant, or supported by other HRQoL data captured during the trial.</p>
<p><u>Adverse events costs</u> (November 2015 PSD, paragraph 7.10).</p> <p>The PBAC noted the toxicity profile of vinflunine and that doubling the cost of treating AEs associated with vinflunine + BSC (from \$██████ to \$██████) but not changing the cost of treating BSC AEs (\$5,415), increased the cost/QALYG from \$45,000 – \$75,000 to \$45,000 – \$75,000.</p> <p>The PBAC also noted that:</p> <ul style="list-style-type: none"> <li>• The proportion of patients hospitalised rather than the number of hospitalisations was used.</li> <li>• The costs for treating the more serious events were not included.</li> <li>• Only the cost of specialist visits has been included for AEs treated outside the hospital setting.</li> </ul> <p>( November 2015 PSD, paragraph 6.24 Table 8).</p>	<p>The resubmission no longer used treatment specific costs for hospitalised AEs for patients in the different treatment arms. Instead the resubmission applied the same cost (\$██████) per hospitalised adverse event across the treatment arms.</p>
<p><u>Cost to PBS/MBS</u> (PSD November 2015, paragraph 7.11).</p> <p>The PBAC noted that the resubmission estimated that ██████ patients would be treated over 5 years at a cost to PBS/MBS of \$10 – \$20 million. The PBAC noted that the DUSC considered that there is potential for the net cost/year for the PBS to be less</p>	<p>The resubmission argued that among the 2nd-line eligible patient group (i.e., only those who had not previously received adjuvant/neoadjuvant chemotherapy and have a PS of one or less) the uptake rate of vinflunine is assumed to be high</p>

Matters of concern	How the resubmission addressed it
than the estimate in the resubmission given that the number of eligible patients has potentially been overestimated, based on the proposed restriction. However, countering this, the PBS costs associated with treating vinflunine adverse events were not considered.	(90%) because of the lack of other treatment options available. The financial model in the resubmission was updated to reflect ESC and PBAC concerns; price has been lowered.

AE: adverse event; BSC: best supportive care; HRQoL: health related quality of life; ICER: incremental cost-effectiveness ratio; ITT: intention to treat; MBS: Medicare benefits schedule; mITT: modified intention to treat; OS: overall survival; PBS: pharmaceutical benefits scheme; QALY: quality adjusted life year; RCT: randomised controlled trial; TCCU: transitional cell carcinoma of the urothelial tract; VFL: vinflunine. Source: Compiled during the evaluation.

## 4 Population and disease

- 4.1 Cancer of the urothelium, known as transitional cell carcinoma of the urothelial tract or TCCU, represents greater than 90% of diagnosed bladder cancers. In invasive or metastatic TCCU, cancer that begins in the urothelial cells may spread through the lining of the bladder and invade the muscle wall of the bladder or spread to nearby organs such as the prostate, uterus, vagina, pelvic or abdominal wall and lymph nodes. Clinical management of advanced or metastatic TCCU typically involves surgery, chemotherapy and radiotherapy.
- 4.2 The resubmission proposed vinflunine as a treatment option for patients with advanced or metastatic TCCU who have failed treatment with chemotherapy regimens containing a platinum compound.

## 5 Comparator

- 5.1 The resubmission nominated two comparators: active chemotherapy and best supportive care (BSC). This is unchanged from the previous submissions.
- 5.2 The PBAC previously considered that “Whilst BSC is an appropriate comparator in determining the efficacy of vinflunine, it is not relevant in Australian clinical practice as vinflunine will likely replace or defer other drugs. The PBAC considered that current standard of care is preferable for the determination of relative effectiveness and therefore the translatability of the trial data to the proposed use in Australia is an area of significant uncertainty.” (PSD, November 2015, paragraph 7.3).
- 5.3 The resubmission made no clinical claim for vinflunine compared to active chemotherapy, and did not present an economic evaluation. The resubmission provided an updated literature search but did not identify any new supporting evidence on chemotherapy comparisons.

## 6 Consideration of the evidence

### **Sponsor hearing**

6.1 There was no hearing for this item.

### **Consumer comments**

6.2 No consumer comments were received for this item.

### **Clinical trials**

6.3 The resubmission was based on one direct head-to-head randomised trial (Study 302) comparing vinflunine + BSC to BSC (n=370). This trial was presented in both previous submissions.

6.4 The resubmission presented additional evidence regarding safety. Seven new citations confirmed safety issues previously reported in Study 302 and two single-arm studies (Study 202 and Study CA001).

6.5 Details of the randomised trial presented in the resubmission is provided in Table 3.

**Table 3: Randomised trial and associated reports presented in the resubmission**

Trial	Report	Publication citation
Direct randomised trials		
Study 302	Study reports Prospective, Randomised phase III Trial of IV Vinflunine plus Best Supportive Care as Second-Line Therapy versus Best Supportive Care after a Platinum-containing Regimen, in Patients with Advanced Transitional Cell Carcinoma of Urothelial Tract: Final Report.	December 2007 (November 2006 analysis) CSR
	Publications Bellmunt, J., Theodore, C., et al. "Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract." (November 2006 analysis)	Journal of Clinical Oncology (2009) 27(27): 4454-4461
	Bellmunt, J., et al. "Long-term survival results of a randomised phase III trial of vinflunine plus best supportive care versus best supportive care alone in advanced urothelial carcinoma patients after failure of platinum-based chemotherapy." (November 2008 analysis)	Annals of oncology (2013) 24.6 (2013): 1466-1472
	Bellmunt Molins, J., et al. "Randomised phase III trial of vinflunine (V) plus best supportive care (B) vs. B alone as 2nd line therapy after a platinum-containing regimen in advanced transitional cell carcinoma of the urothelium (TCCU)."	ASCO Annual Meeting Proceedings (2008) Vol. 26. No. 15_suppl
	Bellmunt, J., Choueiri, T. K., et al. "Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens."	Journal of Clinical Oncology (2010) 28(11): 1850-1855
	Von Der Maase, H., James, N., et al. "Multicentre phase III trial comparing vinflunine (V) plus best supportive care (BSC) vs. BSC alone as 2nd line therapy after a platinum-containing regimen, in advanced transitional cell carcinoma of the urothelium (TCCU)."	Annals of Oncology (2008) 19(S8): viii202
	Harshman, L. C., et al. "The impact of prior platinum therapy on survival in patients with metastatic urothelial cancer receiving vinflunine."	British journal of cancer (2013) 109.10: 2548-2553

Source: Table 2, COM 11-2015

Note: No new publications since the 2015 resubmission.

6.6 Key features of the direct head-to-head randomised trial (Study 302) are summarised in Table 4.

**Table 4: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Vinflunine + BSC vs. BSC						
Study 302	370	R, OL, MC, Median follow-up: vinflunine + BSC = 42 months; BSC = 45 months	Low	Failed platinum based chemotherapy (first-line); PS 0 or 1; not received adjuvant/neoadjuvant chemotherapy treatment.	OS, PFS, EORTC QLQ-C30	Used

DB: double blind; MC: multi-centre; OL: open label; OS: overall survival; PFS: progression-free survival; R: randomised. Source: Compiled during the evaluation and COM 11-2015.

### Comparative effectiveness

6.7 The results presented are unchanged from previous submissions. Progression-free survival and overall survival results from Study 302 are summarised in Table 5 for the intent-to-treat (ITT) and modified ITT (mITT) populations. Kaplan-Meier plots are presented in Figure 1 of the section ‘Economic analysis’ below.

**Table 5: Results of overall and progression-free survival in the direct randomised trial (Study 302)**

	ITT		Modified ITT	
	Vinflunine + BSC N=253	BSC N=117	Vinflunine + BSC N=249	BSC N=108
OS analysis (Cut-off 30 Nov 2008)				
No. of events	237	115	234	108
No. censored (%)	16 (6.3)	2 (1.7)	15 (6.0)	0
Median (95% CI) (months)	6.9 (5.7, 8.0)	4.6 (4.1, 6.6)	6.9 (5.7, 8.0)	4.3 (3.8, 5.4)
HR (95% CI)	0.88 (0.70, 1.10)		0.78 (0.61, 0.96)	
p value	0.2613		0.0227	
PFS analysis				
	ITT		Response evaluable population <sup>a</sup>	
No. of events	237	115	203	93
No. censored (%)	16 (6.3)	2 (1.7)	12 (5.6)	0
Median (95% CI) (months)	2.8 (2.4, 3.4)	1.4 (1.4, 1.5)	3.0 (2.7, 4.1)	1.4 (1.4, 1.5)
HR (95% CI)	0.58 (0.47, 0.73)		0.41 (0.32, 0.53)	
p value	<0.0001		<0.0001	

BSC: Best Supportive Care; CI: confidence interval; HR: hazard ratio; ITT: intent-to-treat; mITT: modified intent-to-treat; OS: overall survival. Notes: a. Defined as per protocol plus remained on study until the first evaluation and received a minimum of two cycles/42 days of treatment, unless progression or early death, and all baseline lesions were to have been assessed with the same method of measurement as baseline. Source: Table 4 and Table B.6.2 COM 11-2015.

6.8 A total of 248 patients received at least 1 dose of vinflunine. In this group, 182 patients received 280 mg/m<sup>2</sup> as their initial dose and 66 patients received 320 mg/m<sup>2</sup> as their initial dose. The efficacy results in Table 5 combine the results of the two dose groups.

6.9 The mITT population excluded 13 patients (4 [1.6%] from the vinflunine + BSC arm and 9 [7.7%] from the BSC arm) post-randomisation who did not meet the key trial inclusion and exclusion criteria. The 2015 resubmission considered the mITT

population to be the most relevant population because the 13 excluded patients would not be eligible under the proposed PBS listing.

6.10 The ESC noted that the 13 patients were excluded from the mITT population for at least one of the following reasons (Table 2, p1469, Bellmunt, J., et al. 2013):

- more than one line of chemo (n=1);
- no locally advanced or metastatic histologically proven transitional cell carcinoma of the urothelium (TCCU) at study entry (n=2);
- no progression after first-line platinum-containing chemotherapy for advanced disease (n=12); and
- received neoadjuvant or adjuvant chemotherapy (n=10).

The ESC considered that in the clinical practice setting, patients requiring treatment with vinflunine may also fall under one of the above criteria, and as such, the ESC considered the ITT population to be the preferred basis to assess clinical efficacy and cost effectiveness. The PBAC agreed with the ESC's views, and also considered that post-hoc exclusion of patients after randomisation was inappropriate due to the high risk of selection bias.

6.11 The 2015 resubmission used the mITT population in the economic evaluation. At its November 2015 meeting, the PBAC considered the results were highly uncertain as they were based on the eligible ITT [mITT] population rather than the ITT population. The PBAC recommended that a major resubmission would need to apply the assessment of the comparative clinical effectiveness and cost effectiveness of vinflunine versus best supportive care using the ITT trial population (PSD November 2015, paragraph 7.12).

6.12 The pre-PBAC response (p1) argued that despite the PBAC's concerns regarding bias associated with the mITT population, the submission presented an otherwise robust estimate of the ICER/QALY.

6.13 The PBAC noted the p value for the ITT results showed a non-significant ( $p=0.2613$ ) and quantitatively small improvement in median survival. The PBAC considered that these small differences observed in the ITT analysis may be due to chance and may not be realised in the clinical practice setting. The PBAC considered noted that the mITT analysis was post-hoc and considered that this was subject to bias.

### ***Comparative harms***

6.14 A summary of the adverse events reported in Study 302 is presented in Table 6. This is unchanged from the previous resubmission.

**Table 6: Results of AEs in the direct randomised trial (Study 302)**

	VFL+BSC (N=248)	BSC (N=117)	VFL+BSC vs. BSC			Initial VFL dose 280 mg/m <sup>2</sup> (N=182)	Initial VFL dose 320 mg/m <sup>2</sup> (N=66)
			RR (95% CI)	RD (95% CI)	NNH (95% CI)		
AEs	248 (100.0)	117 (100.0)	1	0	n.c.	182 (100.0)	66 (100.0)
SAEs	153 (61.7)	55 (47.0)	1.31 (1.06, 1.63)	0.15 (0.04, 0.26)	6.81 (26.32, 3.91)	113 (62.1)	40 (60.6)
Deaths within 30 days <sup>a</sup>	28 (11.3)	27 (23.1)	0.49 (0.30, 0.79)	-0.12 (-0.20, -0.03)	-8.48 (-4.90, -31.25)	25 (13.7)	3 (4.5)
AEs leading to discontinuation	56 (22.6)	8 (6.8)	3.30 (1.63, 6.70)	0.16 (0.09, 0.23)	6.35 (11.36, 4.41)	40 (22.0)	16 (24.2)

AE: adverse event; BSC: best supportive care; CI: Confidence Interval; n.c.: not calculable. NNH: number needed to harm; RR: relative risk; RD: risk difference; SAE: serious adverse event; VFL: vinflunine. Notes: a. Within 30 days of the last dose (VFL+BSC group) or within 30 days of the last visit (BSC group). Source: Table B.6.3, COM 11-2015

6.15 Adverse events that were experienced by at least 10% of the patient population, and at a statistically significantly higher rate in those receiving vinflunine compared with BSC, were abdominal pain, constipation, diarrhoea, nausea, stomatitis, vomiting, fatigue, injection site reactions, weight decrease, anorexia, myalgia, headaches, peripheral sensory neuropathy and alopecia. The Grade III/IV adverse events experienced at higher rates in the vinflunine arm were abdominal pain, constipation, nausea, vomiting, fatigue, infestations and infections, anorexia, myalgia and headache.

6.16 One death due to pancytopenia was reported as directly related to vinflunine. Sixteen patients (6%) in the vinflunine group, and 1 patient (1%) in the BSC group, died within 30 days of either the final vinflunine dose (for the intervention arm) or the final visit (for the BSC arm) for reasons other than progressive disease.

### **Benefits and harms**

6.17 A summary the comparative benefits and harms for vinflunine + BSC versus BSC for the ITT and mITT is presented in Table 7.

**Table 7: Summary of comparative benefits and harms for vinflunine + BSC and BSC**

Benefits						
OS: Study 302, November 2008 cut-off, ITT						
	VFL + BSC	BSC	Absolute Difference	HR (95% CI)		
Survival <sup>a</sup>	237/253	115/117	-	0.88 (0.70, 1.10)		
Median (months)	6.9 (5.7, 8.0)	4.6 (4.1, 6.6)	2.3	-		
OS: Study 302, November 2008 cut-off, mITT						
	VFL + BSC	BSC	Absolute Difference	HR (95% CI)		
Survival <sup>a</sup>	234/253	108/117	-	0.78 (0.61, 0.96)		
Median (months)	6.9 (5.7, 8.0)	4.3 (3.8, 5.4)	2.6	-		
Harms						
	VFL + BSC	BSC	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				VFL + BSC	BSC	
Study 302 (all patients evaluable for safety), Grade 3 or 4 events only						
Febrile neutropenia	15/248	0	14.69 (0.89, 243.43)	6.0	0	0.06 (0.03, 0.09)
Infections with severe neutropenia	16/248	0	9.95 (0.59, 168.40)	6.5	0	0.04 (0.01, 0.07)
Myocardial infarction/ ischaemia	10/248	0	9.95 (0.59, 168.40)	4.0	0	0.04 (0.01, 0.07)

BSC: best supportive care; HR: hazard rate ratio; ITT: intent-to-treat; OS: overall survival; PBO: placebo; RD: risk difference; RR: risk ratio; VFL: vinflunine. Notes: a Median duration of follow-up: Study 302 = 42 months (VFL + BSC) and 45 months (BSC) b. Clinically relevant infections (potential bacterial origin). Source: Compiled during the evaluation and Table 6 COM 11-2015.

6.18 On the basis of the head to head trial, the comparison of vinflunine + BSC and BSC did not result in a statistically significant difference in overall survival for the ITT population.

6.19 With the exclusion of 13 patients who did not meet the trial inclusion or exclusion criteria from the analysis, the comparison of vinflunine + BSC and BSC resulted in:

- approximately 2.6 months difference in median overall survival (November 2008 data cut-off, mITT population); and
- for every 100 patients treated with vinflunine + BSC, approximately 2 additional patients would be alive at 2 years (November 2008 data cut-off, mITT population).

On the basis of the head to head trial presented, vinflunine + BSC was more likely to cause serious adverse events compared with BSC alone; for every 100 patients treated with vinflunine + BSC, approximately 15 additional patients will have a serious adverse event. The events included febrile neutropenia, infections with severe neutropenia and myocardial infarction/ischaemia.

### **Clinical claim**

6.20 The resubmission described vinflunine + BSC as superior in terms of comparative effectiveness and inferior in terms of comparative safety over BSC. The PBAC previously (PSD November 2011, Sections 9 and 12 and PSD November 2015, paragraph 7.5):

- ‘accepted that vinflunine is superior in terms of comparative efficacy over BSC but noted that the increment in overall survival is uncertain and, at best, is

between 2.3 (ITT) and 2.6 months (eligible ITT) and was at a cost of significant treatment-related toxicity’;

- ‘agreed that whilst the eligible ITT population may be reasonable to assess the efficacy of vinflunine, the ITT population should be used in considering the effectiveness of vinflunine as the eligibility criteria in the trial are tighter than the PBS restriction criteria and the ITT population more closely approximates the likely PBS population’;
- ‘agreed that vinflunine is inferior in terms of comparative safety over BSC’.

6.21 The resubmission made no clinical claims regarding vinflunine compared to active chemotherapy. The PBAC noted the incremental effectiveness of vinflunine versus alternative active chemotherapy was unknown, but considered it likely to be insignificant.

### **Economic analysis**

6.22 The resubmission provided an updated trial-based economic evaluation of vinflunine versus BSC. The economic evaluation is a partitioned survival analysis based on data from Study 302. The types of economic evaluation presented were a cost-effectiveness analysis (cost per life year gained) and a cost-utility analysis (cost per quality adjusted life year gained). This is unchanged from the previous resubmission in 2015.

6.23 Regarding the 2015 resubmission, the PBAC was concerned that the results were highly uncertain as they were based on the mITT population rather than the ITT population (PSD, November 2015, paragraph 7.6 and 7.9).

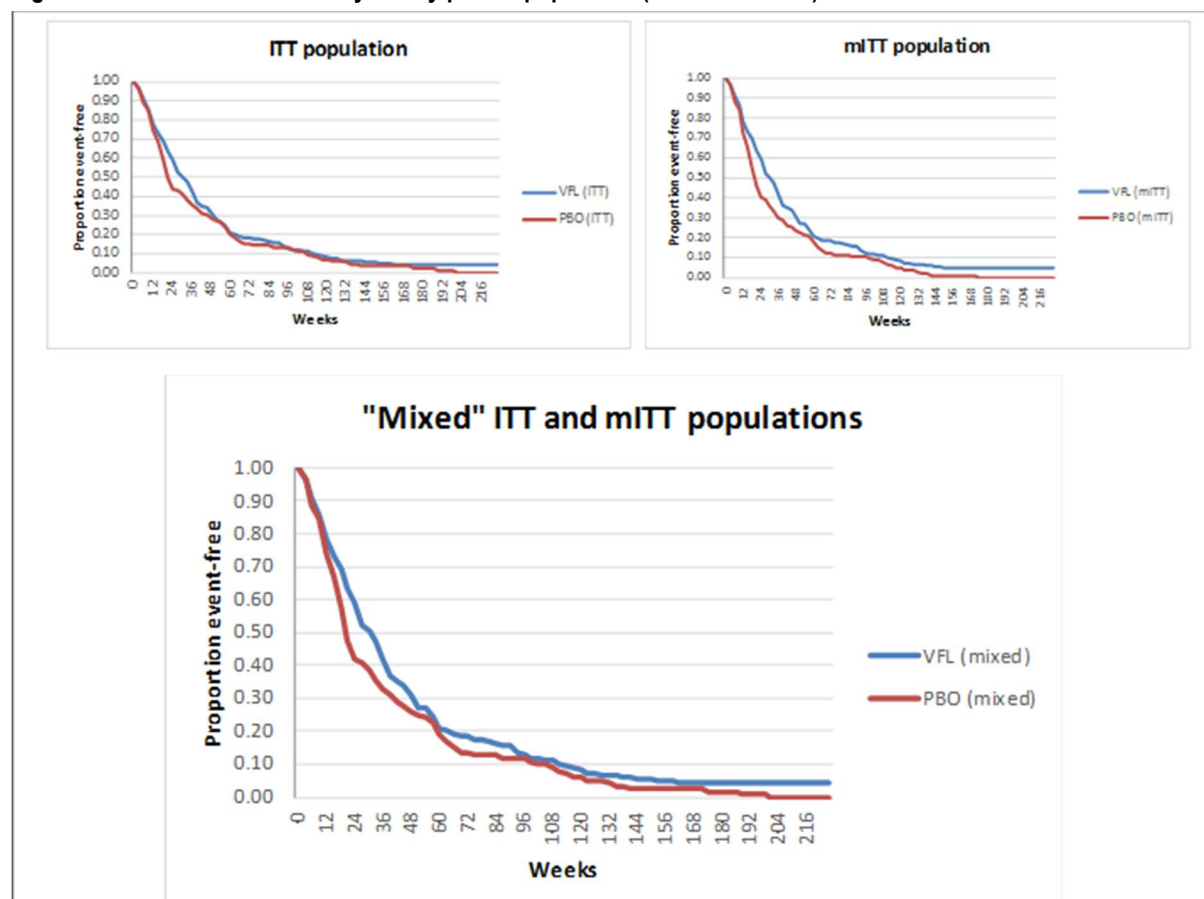
6.24 The resubmission presented a ‘mixed’ estimate of overall survival that lies between the mITT and ITT population (50:50) to address the issue identified by the PBAC. The resulting mean overall survival in the economic model for the ITT, mITT and ‘mixed’ ITT/mITT populations is shown in Table 8.

**Table 8: Overall survival in different population groups**

	ITT		mITT		50:50 ITT and mITT	
	VFL+BSC	BSC	VFL+BSC	BSC	VFL+BSC	BSC
Mean in economic model	11.0	9.5	11.1	8.3	11.1	8.9
Median (95% CI) (Cut-off 30 Nov 2008)	6.9 (5.7, 8.0)	4.6 (4.1, 6.6)	6.9 (5.7, 8.0)	4.3 (3.8, 5.4)	-	-

BSC: best supportive care; ITT: intent-to-treat; mITT: modified intent-to-treat; VFL: vinflunine. Source: Compiled during the evaluation.

Figure 1: Overall survival in Study 302 by patient population (November 2008)



Source: p 25 of the resubmission

- 6.25 Using a 'mixed' estimate of overall survival in the ITT and mITT populations does not address the applicability issue as to whether this population is representative of the proposed Australian population. The updated approach in the resubmission does not address PBAC's concerns regarding bias in the mITT results. The model is sensitive to the population used, in which the exclusion of a small number of patients substantially favours vinflunine + BSC over BSC alone. The ESC and PBAC noted that the gain in overall survival as depicted in the Kaplan Meier plots was marginal.
- 6.26 The PSCR (p2) argued that it is not unreasonable to base an economic evaluation on the patient subgroup expected to access the proposed intervention in Australian practice, and that the mITT population reflects the proposed PBS population. The PSCR (p2) also stated that the 'mixed' ITT/mITT approach was presented as a compromise, as it addresses one of the PBAC's original concerns, that the mITT analysis does not accurately reflect the clinical effectiveness of vinflunine, should the drug leak into patients outside of the proposed restriction criteria. The ESC was of the view that the 'mixed' population weighting approach was not appropriate and favoured vinflunine.

- 6.27 The PBAC recalled that it previously considered that the assessment of the comparative clinical and cost effectiveness of vinflunine versus best supportive care should be based on the ITT trial population. The PBAC agreed with the ESC that the model favoured vinflunine by using results of the ‘mixed’ ITT/mITT population.
- 6.28 The resubmission changed the cost of treating adverse events, other unit costs in the model (PBS, MBS and AR-DRG costs) and the cost of vinflunine compared to the previous submissions.

**Table 9: Summary of model structure and rationale**

Component	Summary
Time horizon	The resubmission stated the time horizon was five years. However, in the model all patients were dead by 4.4 years in the vinflunine + BSC arm and by 3.9 years in the BSC arm.
Outcomes	LYG and QALYG based on a mix (50:50) of ITT and mITT results
Methods used to generate results	Mean survival (PFS and OS) calculated from Kaplan Meier plots from Study 302. A ‘mixed estimate’ was applied for OS of the ITT and mITT population.
Health states	Progression-free disease; Progressive disease and Death
Cycle length	21 days based on vinflunine treatment being administered every 21 days.
Transition probabilities	Partitioned survival analysis used to calculate proportion of patients in each health state

ITT: intent-to-treat; LYG: life years gained; mITT: modified intent-to-treat; OS: overall survival; QALYG: quality adjusted life years gained; VFL: vinflunine. Source: compiled during the evaluation

- 6.29 The key drivers of the model are presented in Table 10.

**Table 10: Key drivers of the model**

Description	Method/Value	Impact
Application of the ‘mixed’ (50:50) mITT and ITT population	A ‘mixed’ estimate of overall survival was based on the ITT and mITT populations (50:50). Use of the ITT population increased the ICER.	High, favours vinflunine + BSC
Pooling of utility values	Utility values for progressive disease were 0.71 in both treatment arms. This is unchanged from the previous submission. Using treatment-specific utilities (VFL+BSC=0.68; BSC=0.74) increased the ICER. The ESC considered use of the pooled utility values for progressive disease was reasonable on the basis that vinflunine treatment is not to be used after progression and the adverse events with vinflunine are usually transient.	Moderate, favours vinflunine + BSC
Treatment cycles	The average number of vinflunine cycles applied in the model was 4.2 based on the clinical trial data. Increasing the number of treatment cycles increased the ICER.	Moderate, favours vinflunine + BSC

BSC: Best Supportive Care; ICER: incremental cost-effectiveness ratio; ITT: intent-to-treat; mITT: modified intent-to-treat. Source: compiled during the evaluation

- 6.30 Results of the stepped economic evaluation and the ICER from the 2015 resubmission are presented in Table 11.

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**Table 11: Results of the stepped economic evaluation**

Step and component	Vinflunine + BSC	BSC	Increment
<b>Step 1: trial-based costs and outcomes (ITT)</b>			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
LYG	0.8484	0.7367	0.1117
Incremental cost/extra LYG gained			
<b>Step 2: trial-based costs and outcomes (ITT:mITT (50:50))</b>			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
LYG	0.8521	0.6883	0.1638
Incremental cost/extra LYG gained			
<b>Step 3: Transform to QALYs</b>			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
QALYs	0.6188	0.5035	0.1153
Incremental cost/extra QALYs gained			
<b>Step 4: Include admin costs</b>			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
QALYs	0.6188	0.5035	0.1153
Incremental cost/extra QALYs gained			
<b>Step 5: Include lab test costs</b>			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
QALYs	0.6188	0.5035	0.1153
Incremental cost/extra QALYs gained			
<b>Step 6: Include laxative tx costs</b>			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
QALYs	0.6188	0.5035	0.1153
Incremental cost/extra QALYs gained			
<b>Step 7: Include PRT costs</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	0.6188	0.5035	0.1153
Incremental cost/extra QALYs gained			
<b>Step 8: Include AE costs</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	0.6188	0.5035	0.1153
Incremental cost/extra QALYs gained			
<b>Step 8: Include medical service costs</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	0.6188	0.5035	0.1153
Incremental cost/extra QALYs gained			
<b>Incremental cost/extra QALYs gained using only the ITT population</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	0.6161	0.5378	0.0783
Incremental cost/extra QALYs gained			
<b>July 2015 resubmission</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	0.6214	0.4692	0.1522
Incremental cost/extra QALYs gained			

AE: adverse event; ITT: intention to treat; mITT: modified intention to treat; PRT: palliative radiotherapy; QALY: quality adjusted life year. Source: Table 36 p48 of the resubmission, Compiled during evaluation. Table D.5.5 of the COM 11-2015.

The redacted table shows ICERs in the range of \$45,000/QALY - \$75,000/QALY

- 6.31 The evaluation considered the ICER may be underestimated due to the use of the 'mixed' population, rather than the ITT population. Furthermore, the ICER may be underestimated as AE costs may be underestimated, the cost of G-CSF for the treatment and prevention of neutropenia was excluded, the submission did not consider the costs of more expensive laxatives, and BSC costs and post-progression costs, such as costs for gemcitabine and hospitalisations, were excluded. The costs of adverse events were based on the proportion of patients hospitalised (rather than the number of events and hence did not account for patients having more than 1 event); the cost of treating more serious events was not included; and only the cost of specialist visits was included for adverse events treated outside the hospital setting. G-CSF is not currently listed on the PBS for this indication, however it was used in Study 302 for patients with febrile neutropenia and for prophylaxis for further cycles.
- 6.32 In relation to the exclusion of G-CSF costs for the treatment and prevention of neutropenia, and the costs of more expensive laxatives, the PSCR (p3) argued that only 6% of patients in the vinflunine arm of the trial experienced febrile neutropenia and that vinflunine does not qualify as chemotherapy regimen with a high risk of neutropenia, according to European Society for Medical Oncology (ESMO) guidelines.
- 6.33 The PSCR (p3) argued that the cost of laxative use was included in the resubmission. The ESC noted the cost of laxatives was included in the submission, however the cheaper option sennoside (\$2.23 patient/cycle) was selected over the more expensive methylnaltrexone (\$263.27 patient/cycle). Applying the cost of methylnaltrexone in the economic model increased the ICER/QALY gained to \$45,000 - \$75,000.
- 6.34 The ESC noted that the resubmission provided an updated approach to estimating the cost of adverse events, which was further highlighted in the PSCR (p2-3). The ESC considered that this new approach, which increases the comparability in cost of AEs between the vinflunine and BSC arms, is more reasonable than the approach applied in the 2015 resubmission. However, the ESC agreed with the evaluation that there were relevant costs that were excluded (as stated in paragraph 6.30 above), which may have underestimated the overall AE costs.
- 6.35 The model is most sensitive to the population used. The PBAC noted that use of the ITT population rather than the 'mixed' ITT/mITT population increased the ICER to \$75,000 – \$105,000/QALY gained.
- 6.36 The cost per QALY in the resubmission (\$45,000 – \$75,000) was lower than in the November 2015 submission (\$45,000 – \$75,000) primarily due to a reduction in the price of vinflunine. The PBAC noted that the use of the 'mixed' ITT/mITT population, updated unit costs and hospitalisations costs increased the ICER to \$45,000 – \$75,000/QALY. Inclusion of the reduced price of vinflunine resulted in an ICER of \$45,000 – \$75,000/QALY.

6.37 The ESC noted that to achieve an ICER/QALY gained of \$45,000 – \$75,000 using results of the ITT population, the price of vinflunine would need to be \$█/mg. This represents a 63% price reduction from the cost of vinflunine in the current resubmission (\$█/mg). The PBAC noted this analysis but this did not obviate concerns regarding the clinical data informing the model.

**Drug cost/patient/year (average 4.2 cycles): \$█**

6.38 The dispensed cost per cycle for vinflunine is \$█ based on the effective ex-manufacturer vial prices, the dose from Study 302 and 75% use in private hospitals (1.56 x \$█ + 1.941 x \$█ + 0.75 x \$█ + 0.25 x \$█).

**Estimated PBS usage & financial implications**

6.39 This resubmission was not considered by DUSC. The resubmission used an epidemiological approach to estimate the financial implications of listing vinflunine on the PBS. A number of variable and model inputs were revised, but the approach used was generally the same as for the November 2011 and November 2015 resubmissions.

**Table 12: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated (90% uptake)	█	█	█	█	█
Number treated (90% uptake)- Nov 2015	█	█	█	█	█
Vials	█	█	█	█	█
Vials - Nov 2015	█	█	█	█	█
Estimated net cost to PBS/MBS					
Net cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█
Net cost to PBS/RPBS Nov 2015	\$█	\$█	\$█	\$█	\$█
Net cost to MBS at 85% benefit*	-\$█	-\$█	-\$█	-\$█	-\$█
Net cost to MBS Jul 2015 at 85% benefit	-\$█	-\$█	-\$█	-\$█	-\$█
Estimated total net cost					
Net cost PBS/MBS	\$█	\$█	\$█	\$█	\$█
Net cost PBS/MBS Nov 2015	\$█	\$█	\$█	\$█	\$█

Notes: \*From the Section E model. Net cost to MBS = sum of MBS of admin procedures and palliative radiotherapy.

Source: Table 56 p 66 of the resubmission and Table E.5.1 COM 11-2015 and calculated during the evaluation.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than \$10 million.

6.40 There is potential for the net PBS cost/year to differ from that estimated in the submission given uncertainty in the uptake of vinflunine (90%), which was based on a survey of three oncologists. The PSCR (p4) stated that vinflunine has a TGA orphan designation, which reflects the rarity of the condition and paucity of relevant epidemiological data. The PSCR (p4) acknowledged that the vinflunine uptake may be overestimated, however stated that in calculating the proportion of patients with previous neoadjuvant/adjuvant chemotherapy use (noted as approximately 40%), the evaluators assumed all patients diagnosed with localised or regional TCCU would receive neoadjuvant/adjuvant chemotherapy, which was likely overestimated. The

PSCR (p4) argued that patients diagnosed with localised or regional disease who experienced disease progression may be less likely to meet eligibility criteria related to performance status (i.e., have a PS  $\leq$  1) than patients diagnosed with advanced or metastatic disease. The PSCR (p4) argued that this will mitigate any overestimation of vinflunine patients in the financial impact model. The ESC agreed with the evaluation that the estimated uptake was uncertain, and considered that the 90% uptake rate was optimistic given that the efficacy of vinflunine was marginal and that any survival gain was at the expense of increased toxicity. The PBAC agreed with the ESC's views.

### **Financial Management – Risk Sharing Arrangements**

- 6.41 The resubmission stated that it “maintained the mITT analysis as the appropriate analysis given the safeguards against inappropriate use of vinflunine proposed (e.g. authority required and financial risk share/caps)”. However no risk-sharing arrangement involving caps was detailed in the submission.

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend listing vinflunine on the PBS for the treatment of locally advanced or metastatic transitional cell carcinoma of the urothelial tract (TCCU), on the basis of lack of evidence of an incremental gain in overall survival versus currently available alternative active chemotherapy. The PBAC further noted that compared with best supportive care (BSC) the incremental benefit was small for both overall survival and progression free survival. Further concerns related to the significant toxicity of the drug. The PBAC concluded that the cost-effectiveness ratio was high and underestimated in the submission.
- 7.2 Regarding the proposed restriction, the PBAC considered, as it did in 2015, that the exclusion of patients who had received neoadjuvant or adjuvant treatment would likely exclude otherwise eligible patients who may derive a benefit from treatment with vinflunine.
- 7.3 The PBAC recalled its previous decision that alternate active chemotherapy such as taxanes was a relevant comparator. The PBAC noted that although the resubmission nominated active chemotherapy as a comparator, the clinical effectiveness and cost effectiveness of active chemotherapy compared to vinflunine was not presented. The PBAC considered the incremental benefit of vinflunine versus alternative chemotherapy regimens would be smaller than for vinflunine versus BSC, and likely to be clinically insignificant.
- 7.4 The PBAC noted, as for the November 2011 and November 2015 submissions, the resubmission presented one randomised, unblinded trial (Study 302), comparing vinflunine (280 mg/m<sup>2</sup> or 320 mg/m<sup>2</sup> every three weeks) and BSC with BSC alone in patients with advanced or metastatic TCCU after failure of a prior platinum-containing regimen as the key clinical evidence. The PBAC noted that additional

information regarding the safety of vinflunine was provided in the resubmission, and the reported adverse events were consistent with those reported in the key clinical trial.

- 7.5 On the basis of the unchanged primary evidence, the PBAC noted its previous acceptance that vinflunine is superior in terms of comparative efficacy over BSC, but the Committee maintained its concern that the incremental gain in overall survival (non-significant gain in median overall survival of 2.3 months for the ITT population) is modest, uncertain, may not be realised in clinical practice, and was at the expense of significant treatment-related toxicity. The PBAC agreed that vinflunine is inferior in terms of comparative safety versus best supportive care.
- 7.6 The PBAC maintained its views from November 2011 and November 2015 that the ITT population should be the basis for assessing the clinical and cost effectiveness of vinflunine versus BSC. The PBAC considered the results of the mITT analysis to be biased due to the post-hoc removal of patients from the analysis. The PBAC also considered that the ITT population more closely approximates the potential PBS population than the mITT population..
- 7.7 The PBAC noted that there was no clinical rationale to justify the use of the 50:50 ITT/mITT analysis, and that the submission applied this approach as a compromise between the Committee's views and the sponsor's views. The PBAC considered that use of the mixed ITT/mITT population in the economic model, which resulted in an ICER/QALY gained of \$45,000 – \$75,000 compared to \$75,000 – \$105,000 if the ITT population was used, favoured vinflunine. The PBAC considered that the cost-effectiveness ratio for the ITT population was high and highly uncertain, given the Committee's concerns about the uncertainty in the incremental gain in overall survival of vinflunine over BSC.
- 7.8 The PBAC noted the sponsor's willingness to enter a risk-share agreement, however, the PBAC considered that the estimated PBS usage and financial implications were uncertain and likely overestimated, as it expected that there will be limited use of vinflunine given its uncertain clinical benefit and significant toxicity.
- 7.9 The PBAC recognised there is an unmet clinical need for patients with locally advanced or metastatic TCCU, however did not consider that vinflunine provides superior outcomes to the currently available treatments, such as alternate active chemotherapy.
- 7.10 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## **9 Sponsor's Comment**

The sponsor had no comment.