

Title: Fludara in first-line CLL
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Fludarabine phosphate for the first-line treatment of Chronic Lymphocytic Leukaemia

Additional analysis in response to questions B10 & B12 from the
Evidence Review Group

Academic in Confidence Data

[This version of the STA document has had all 'academic in confidence' data removed.](#)

Schering Health Care Ltd

20th July 2006

Contact



Summary

The initial NICE response to the Fludarabine STA submission contained a question (B10) relating to treatment of overall survival in the model and a second question (B12) requesting a graphical presentation of the sensitivity analysis. This document reports additional analysis conducted in response to question B10 and displays the results in graphical format as requested in question B12.

Questions from NICE:

- B10. Please provide additional clarification on the calculations used to make overall survival equivalent for each strategy (Question 82, page 94 of main submission). In particular we are unclear how the survival equalisation approach takes account of the additional time in the response rate for patients retreated with F or FC. Similarly we are unclear how the approach adjusts for the differential mortality rates in 'observed' patients. Finally we have set utility values for all states to be 1 (i.e. an analysis based on LYG) - we would assume that outcomes would be equivalent if survival were equivalent across the strategies. However, there appear to be major differences in the LYG calculations. Please clarify why this is so.
- B12. Please provide a visual/graphical representation of the results of the one-way sensitivity analyses (Table 54, pages 133-134 of main submission), for example a tornado diagram. We would like to evaluate the relative impact of the different uncertainty parameters on cost effectiveness.

Response (B10)

In the economic model and accompanying report provided with the STA submission of June 2006, overall survival for patients in the fludarabine and chlorambucil arms was adjusted. This was done by extending median survival in the final progressive disease state to offset the fact that these patients have a lower median duration of response at first line. The survival equalisation approach did not make correction for differences in duration of response at second line or later. This approach also addressed only median survival, which may give different results than calculations of mean survival.

To address question B10 we re-calculated the model to give equal mean life years in all arms. This was done by changing the time spent in the final progression state for the fludarabine and chlorambucil arms so that, when all utility states were set to the value one, life years gained were equal for all three arms.

The following results were calculated based on this revised methodology:

- Base case costs and effectiveness
- Subgroup analyses by age and staging
- One-way and stochastic sensitivity analyses
- Scatter plots and CEACs
- Budget impact analysis

Results

Table 1: Base case cost and effectiveness findings (cohort of 1,000)

Treatment strategy	Costs	Outcomes (QALYs)
CLB 1st line	£ 11,920,074	5248
F 1st line	£ 17,712,428	5469
FC 1st line	£ 13,919,492 ¹	5864

Table 2: Comparisons between therapies

Incremental	Costs	Outcomes (QALYs)	C/E ratio
F 1st line vs CLB 1st line	£ 5,792,354	222	£ 26,105
FC 1st line vs CLB 1st line	£ 1,999,418	616	£ 3,244
FC 1st line vs F 1st line	-£ 3,792,936	394	Dominant

Table 3: PSA findings: costs and outcomes

	Costs	Outcomes	
CLB	£11,920	5.25	
95% CI	(£10400, £13683)	(4.84, 6.49)	
F	£17,712	5.47	
95% CI	(£15587, £20532)	(4.95, 6.78)	
FC	£13,919	5.86	
95% CI	(£12301, £15760)	(5.26, 7.35)	
Incremental	Costs	Outcomes	C/E ratio
F vs CLB	£5,792	0.22	£26,105
95% CI	(£3250, £8909)	(-0.31, 0.73)	(£-210608, £206922)
FC vs CLB	£1,999	0.62	£3,244
95% CI	(£-303, £4372)	(-0.09, 1.46)	(£-9872, £14598)
FC vs F	-£3,793	0.39	-£9,616
95% CI	(£-6786, £-1267)	(-0.36, 1.28)	(£-141972, £62966)

¹ In the course of making these changes a calculation error in the FC arm was identified and corrected. Fixing this error increased expected cost in the FC arm by almost 2%, from £13657 to £13919 per patient.

Figure 1: Incremental costs and outcomes per 1,000 patients
Fludarabine compared to chlorambucil

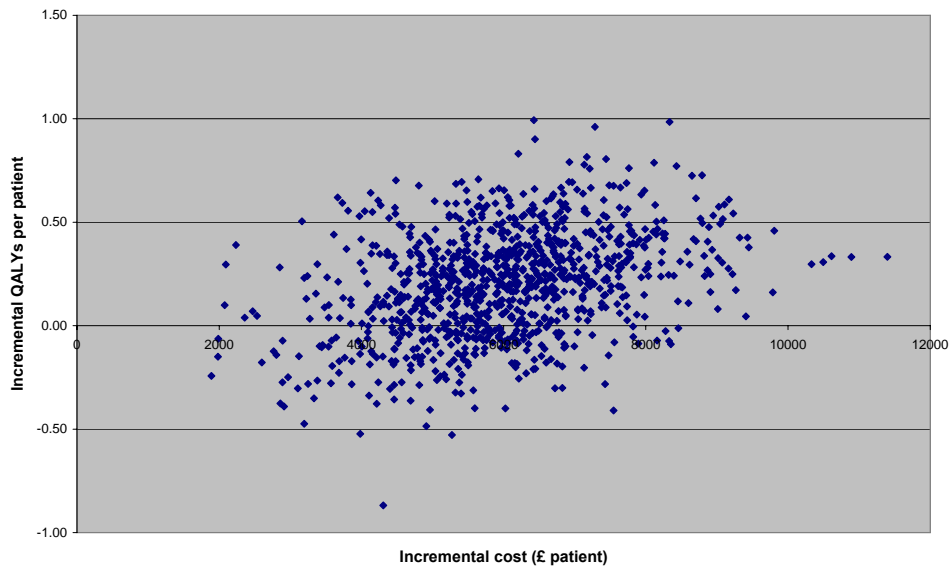


Figure 2 Incremental costs and outcomes per 1,000 patients
FC compared to chlorambucil

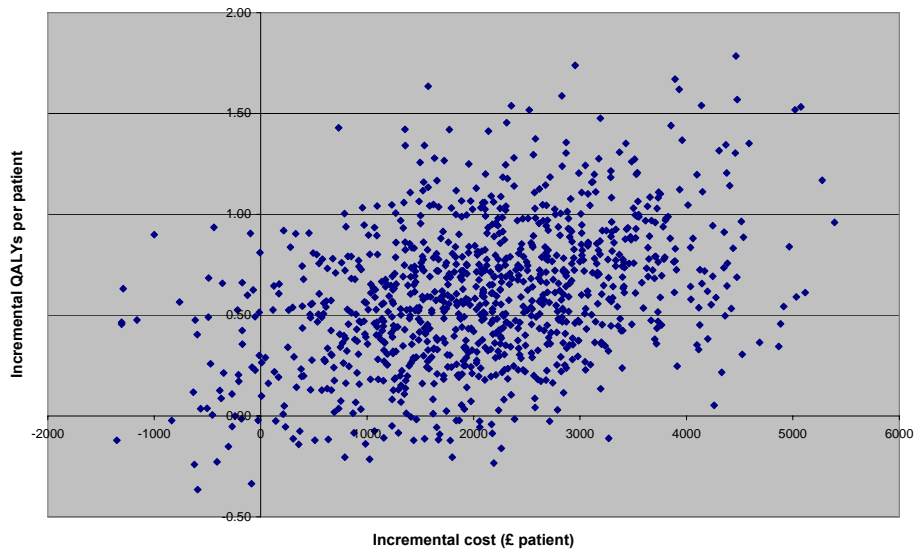
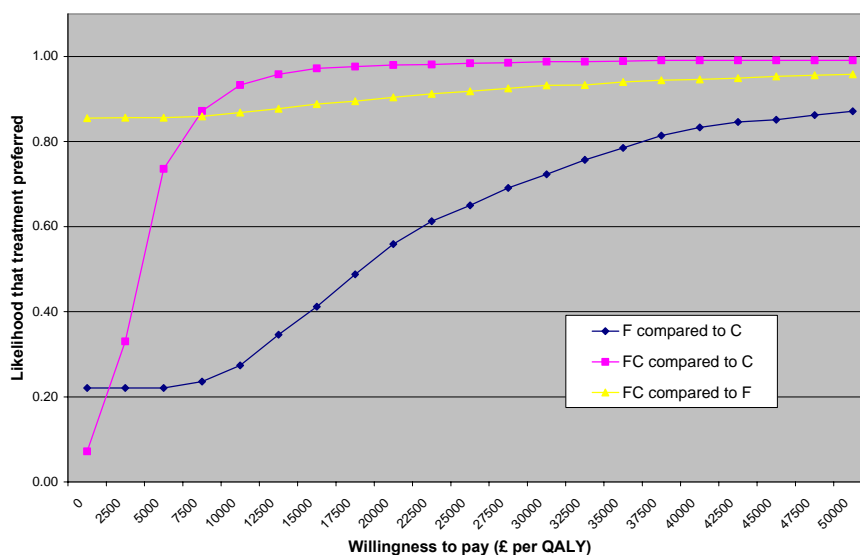


Figure 3: Cost-effectiveness acceptability curve



The results of the sub-group analysis are presented below. For each subgroup, the time in final progression was adjusted to ensure that the mean survival for the subgroup analysis remained equal for the three treatments. In addition, in the subgroup analyses by age, age on entry to the model was adjusted to reflect the average age in the sub-group cohort.

Table 4: Subgroup analysis for fludarabine patients by age (cohort 1,000)

	Fludarabine		Chlorambucil		ICER
	Costs	QALYs	Costs	QALYs	
Age >=65	£15,363,339	4633	£10,060,707	4411	£23,923
Age <=64	£20,289,703	6495	£14,105,843	6279	£28,666

Table 5: Subgroup analysis for FC patients by age (cohort 1,000)

	Fludarabine + cyclophosphamide		Chlorambucil		ICER
	Costs	QALYs	Costs	QALYs	
Age >=65	£11,542,847	4828	£10,060,707	4411	£3,556
Age <=64	£16,750,918	7164	£14,105,843	6279	£2,989

Table 6: Subgroup analysis by Binet stage at baseline (cohort 1,000)
 Fludarabine relative to chlorambucil

	Fludarabine		Chlorambucil		ICER
	Costs	QALYs	Costs	QALYs	
Binet Stage A+	£17,766,739	5254	£11,395,804	5086	£37,933
Binet Stage B	£18,933,937	5982	£12,631,558	5621	£17,444
Binet Stage C	£15,747,525	4883	£11,337,116	4848	£128,561

Table 7: Subgroup analysis by Binet stage at baseline
 FC relative to chlorambucil

	Fludarabine + cyclophosphamide		Chlorambucil		ICER
	Costs	QALYs	Costs	QALYs	
Binet Stage A+	£12,959,858	5508	£11,395,804	5086	£3,709
Binet Stage B	£14,986,995	6381	£12,631,558	5621	£3,099
Binet Stage C	£13,108,177	5423	£11,337,116	4848	£3,085

Table 8: Findings of one-way sensitivity tests

Sensitivity tests	Fludarabine		Chlorambucil		FC		F - CLB	FC-CLB
	Costs	QALYs	Costs	QALYs	Costs	QALYs	C/E ratio	C/E ratio
Base case	£17,712,428	5469	£11,920,074	5248	£13,919,492	5864	26105	3244
FC followed by FCR	£17,712,428	5469	£11,920,074	5248	£16,559,966	5944	26105	6659
CLB followed by FC	£17,712,428	5469	£11,598,475	5306	£13,919,492	5864	37470	4162
Re-treat if response \geq 6 months	£17,868,166	5479	£11,777,072	5224	£13,984,100	5871	23853	3411
Response rates at 1 st line from literature	£19,711,444	5980	£13,246,049	5409	£16,027,517	6635	11313	2268
F re-treat: response rate upper limit	£17,777,136	5555	£11,920,074	5248	£13,919,492	5864	19036	3244
F re-treat: response rate lower limit	£17,627,340	5357	£11,920,074	5248	£13,919,492	5864	52331	3244
CLB re-treat: response rate upper limit	£17,712,428	5469	£12,011,883	5371	£13,919,492	5864	58164	3874
CLB re-treat: response rate lower limit	£17,712,428	5469	£11,846,010	5148	£13,919,492	5864	18229	2895
FC re-treat: response rate upper limit	£17,712,428	5469	£11,920,074	5248	£13,963,086	5916	26105	3055
FC re-treat: response rate lower limit	£17,712,428	5469	£11,920,074	5248	£13,876,208	5812	26105	3466
FC after F: response rate upper limit	£17,749,642	5511	£11,920,074	5248	£13,919,492	5864	22107	3244
FC after F: response rate lower limit	£17,673,946	5426	£11,920,074	5248	£13,919,492	5864	32207	3244
F after CLB: response rate upper limit	£17,712,428	5469	£11,932,004	5261	£13,919,492	5864	27775	3298
F after CLB: response rate lower limit	£17,712,428	5469	£11,906,851	5232	£13,919,492	5864	24481	3187
CHOP after FC: response rate upper limit	£17,712,428	5469	£11,920,074	5248	£13,925,004	5869	26105	3225
CHOP after FC: response rate lower limit	£17,712,428	5469	£11,920,074	5248	£13,914,609	5859	26105	3261
Salvage: response rate upper limit	£17,759,794	5511	£11,974,678	5296	£13,955,486	5893	26965	3321
Salvage: response rate lower limit	£17,672,311	5434	£11,873,827	5206	£13,889,006	5839	25420	3183
Salvage data from pooled studies	£17,852,495	5592	£12,081,545	5392	£14,025,932	5949	28831	3486
Response rates on re-treatment equal first line	£17,721,430	5481	£12,044,881	5416	£13,919,492	5864	86770	4185

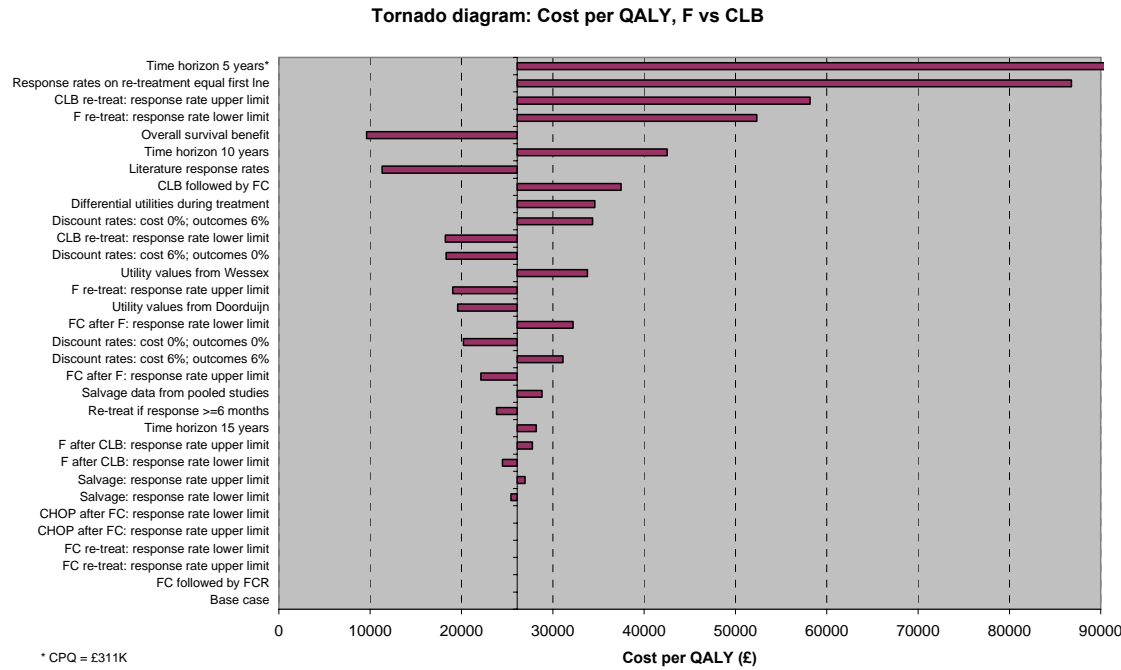
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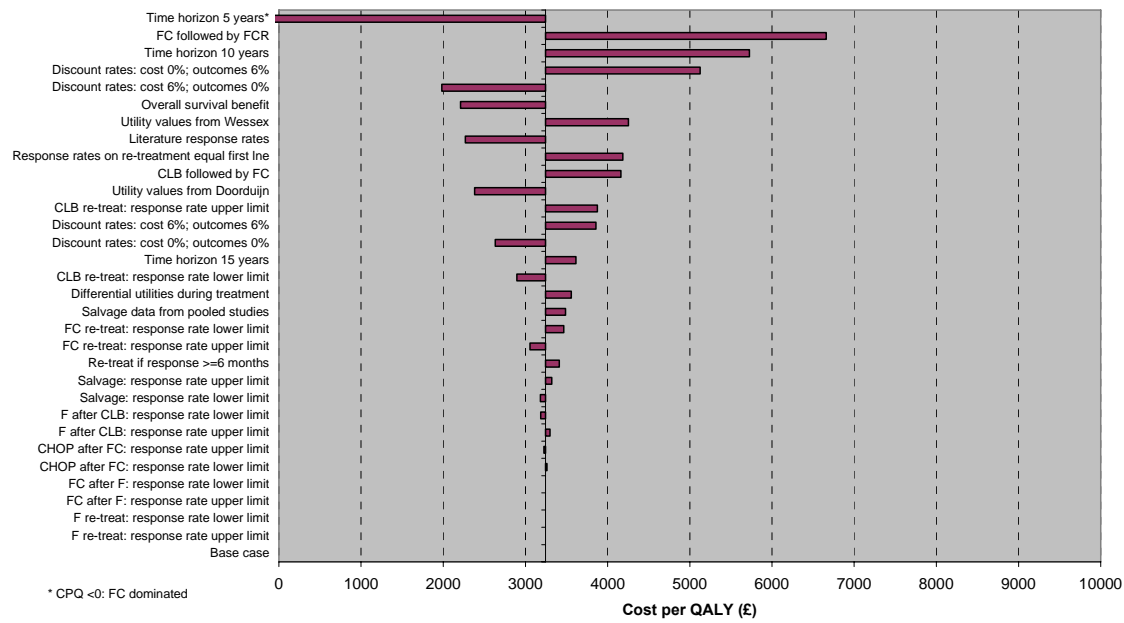
Table 8: Findings of one-way sensitivity tests (continued)

Sensitivity tests	Fludarabine		Chlorambucil		FC		F-CLB	FC-CLB
	Costs	QALYs	Costs	QALYs	Costs	QALYs	C/E ratio	C/E ratio
Base case	£17,712,428	5469	£11,920,074	5248	£13,919,492	5864	£26105	£3244
Utility values from Doorduijn	£17,712,428	5103	£11,920,074	4807	£13,919,492	5647	£19567	£2380
Utility values from Wessex	£17,712,428	6836	£11,920,074	6665	£13,919,492	7135	£33795	£4253
No utility decrement during chlorambucil treatment	£17,712,428	5469	£11,920,074	5302	£13,919,492	5864	£34610	£3559
Removing rapid 'progression to death time' for fludarabine and making equal to chlorambucil	£16,292,083	4643	£9,702,308	3958	£13,919,492	5864	£9610	£2212
Time horizon 5 years	£12,615,447	3192	£7,789,351	3176	£8,803,878	3168	£310663	-£119663
Time horizon 10 years	£16,323,615	4764	£10,822,016	4634	£12,088,776	4855	£42516	£5726
Time horizon 15 years	£17,438,150	5323	£11,696,253	5120	£13,452,029	5605	£28178	£3616
Discount rates: cost 0%; outcomes 6%	£19,924,375	4929	£13,754,422	4749	£16,170,604	5221	£34351	£5124
Discount rates: cost 0%; outcomes 0%	£19,924,375	6462	£13,754,422	6157	£16,170,604	7075	£20223	£2633
Discount rates: cost 6%; outcomes 6%	£16,491,339	4929	£10,901,515	4749	£12,721,298	5221	£31121	£3860
Discount rates: cost 6%; outcomes 0%	£16,491,339	6462	£10,901,515	6157	£12,721,298	7075	£18322	£1983

B12. Please provide a visual/graphical representation of the results of the one-way sensitivity analyses (Table 54, pages 133-134 of main submission), for example a tornado diagram. We would like to evaluate the relative impact of the different uncertainty parameters on cost effectiveness.



Tornado diagram: Cost per QALY, FC vs CLB



Budget impact tables

Table 9: Mean cost per patient starting first-line treatment by year since start of treatment

Time since start of treatment	Cost per patient		
	F	Chl	FC
Year 1	£6,959	£2,404	£4,751
Year 2	£1,335	£1,554	£1,072
Year 3	£1,590	£1,467	£1,041
Year 4	£1,488	£1,322	£996
Year 5	£1,343	£1,121	£1,020

Table 10: Estimated cost per year: "No change" scenario

No. in arm	271	1982	516	
%	9.8%	71.6%	18.6%	
Year	F	Chl	FC	Total
2007	£1,885,850	£4,764,589	£2,451,264	£9,101,703
2008	£2,247,719	£7,844,839	£3,004,368	£13,096,926
2009	£2,678,498	£10,752,887	£3,541,339	£16,972,724
2010	£3,081,634	£13,373,548	£4,055,181	£20,510,364
2011	£3,445,650	£15,594,520	£4,581,548	£23,621,718

Table 11: Estimated cost per year: "FC recommended" scenario

No. in arm	138	415	2215	
%	5.0%	15.0%	80.0%	
Year	F	Chl	FC	Total
2007	£1,926,908	£665,648	£10,523,334	£13,115,890
2008	£2,296,655	£1,095,982	£12,897,821	£16,290,458
2009	£2,736,812	£1,502,258	£15,203,052	£19,442,122
2010	£3,148,725	£1,868,383	£17,408,988	£22,426,097
2011	£3,520,666	£2,178,669	£19,668,691	£25,368,027

Conclusion

A limitation of the cost effectiveness analysis presented in the submission is that the follow up available for first line therapy from the UK CLL4 study is insufficient to demonstrate a difference in overall survival. The model submitted adjusted median survival in the final progressive disease state to offset the gain in median duration of response at first line. This alternative analysis presented here used a revised methodology which instead ensured the mean number of life years gained are equal for all three treatments.

In this alternative analysis, FC remains highly cost effective compared to the current standard of chlorambucil, giving an incremental cost effectiveness ratio (cost per quality adjusted life year) of £3,244. The cost effectiveness of fludarabine versus chlorambucil is estimated to be £26,105.

Lower costs of subsequent treatment with FC treated patients within a 5 year timeframe means that the budget impact at 5 years remains modest (Annual expenditure in year 5 estimated to be £25.4 million vs. £23.6 million.)