

ERG review of responses to the ACD related to assumptions in the economic modelling

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Date completed: 20th of February 2013

The manufacturer of romiplostim has raised a number of concerns about the modelling.

3.1 The odds ratio of 0.15 was not explored.

The manufacturer of romiplostim is correct that this is not within the ERG report, but this was prepared by the ERG for the Appraisal Committee. There is the additional difficulty that the odds ratio of 0.15 is only available for all patients as the models for splenectomised and the non-splenectomised did not converge, and applying this odds ratio within the splenectomised modelling and within the non-splenectomised modelling raises further questions. It seems possible that one or other manufacturer will protest about the pooled response rate not being reasonable to apply for the base case within one or both of the subgroup-specific models, depending upon which manufacturer this favours.

3.2 The time on treatment was assumed to be the same.

This is correct, and the assumption of complete clinical equivalence was drawn attention to in the ERG report (p. 135) as being not limited to response rates, but also to duration of therapy, duration of therapy spent in platelet response and adverse event rates.

But it should also be borne in mind that the time on treatment curves used within the model are specific to eltrombopag responders. Even if response rates differ between eltrombopag and romiplostim, it may not be as unreasonable to assume that the time on treatment for responders would be similar between treatments. The assumption of equal time on treatment among responders does not rely upon the assumption of equal response rates. This is not to say that responders to eltrombopag will not have a different duration of time on treatment than responders to romiplostim, but in the absence of other data it perhaps not as offensive an assumption as suggested by the manufacturer of romiplostim.

Note also that due to the very poor cost effectiveness of the thrombopoietin receptor agonists (TPOs) compared to the non-TPO sequence under the “alternative” analysis, with this worsening still further

when the GSK SF-6D data is applied, it is possible that differentiating the TPO time on treatment among responders will worsen the cost effectiveness of the TPO with the longer duration of treatment among responders. The manufacturer of romiplostim appears to argue that this will be romiplostim.

3.3 Romiplostim drug cost

The numbers of vials presented within the manufacturer of romiplostim submission to the romiplostim single technology appraisal (technology appraisal [TA] 221) were redacted. The revised responder analysis of the manufacturer of romiplostim of 1.54 vials for the splenectomised and 1.10 vials for the non-splenectomised would alter the analysis. The derivation of the 1.54 and the 1.10 cannot be checked by the ERG and it is unclear how it has been arrived at, and whether it is based upon medians or means. The parallel average based upon the ERG analysis of the median dosing data for responders resulted in sensitivity analyses of 1.28 vials for splenectomised and 1.00 vials for non-splenectomised patients.

The ERG sensitivity analysis that applied the romiplostim median doses among responders from Kuter is partial and was noted as such, in that similar arguments may apply to eltrombopag. The mean dose among eltrombopag responders may also be lower, given that the mean dose per patient did vary slightly over the RAISE trial.

The ERG pointed out during first Appraisal Committee meeting that if romiplostim patients reduced their dose by spacing out administrations rather than reducing the dose per administration this could in itself reduce wastage to the point where romiplostim might be cheaper than eltrombopag, based upon the median doses among romiplostim responders.

3.4 The time to response was shorter for eltrombopag

The manufacturer of romiplostim raises a concern about the 15 day time to response for eltrombopag compared to the 28 day time to response for romiplostim. While this is literally correct, the impact within the model is that for both eltrombopag and romiplostim all patients receive one full 4 week cycle of treatment. At the end of this 1st cycle patients are assessed for response, with non-responders then discontinuing treatment; i.e. for both TPOs all non-responders only receive one cycle of treatment. In other words, both TPOs are treated the same for both costs and QALYs in the first cycle of the model.

For instance, for the average drug costs for eltrombopag see table 52 of the ERG report. The 1st cycle drug cost is in line with the subsequent cycles and assumes that eltrombopag patients remain on treatment during the first 4 weeks of the model.

3.5 The health state utilities were not taken from RAISE

The ERG did explore this through univariate sensitivity analyses. The main concern of the manufacturer of romiplostim here seems to be that these were not used for the base case. This is correct, and serves to worsen the cost effectiveness of the TPOs against the non-TPO sequence.

This point need to be read alongside the assertion by the manufacturer of romiplostim that the time spent on romiplostim may be longer than for eltrombopag, though the manufacturer of romiplostim does not take this as far as the average time for responders. But the manufacturer of romiplostim appears to suggest that romiplostim is more effective than eltrombopag. Applying the SF-6D utilities within this context is likely to worsen the cost effectiveness of romiplostim compared to eltrombopag.

3.6 Romiplostim administration cost

The manufacturer of romiplostim is correct to note that £204 per administration is too high a cost. This was an oversight by the ERG due in part to the HRG code SB12Z relating to simple parenteral administration which would seem to encompass subcutaneous administration, and also due in part to the assumed 72% home administration of romiplostim much reducing the average administration cost.

But as the manufacturer of romiplostim correctly points out, the first month of romiplostim administration applies the £204.81 per administration for four romiplostim administrations, which is not reasonable.

More reasonable might be to use the cost per consultant led follow up outpatient visit for clinical haematology of £147.53, though this could still be seen as quite high given other costings within NICE STAs for the likes of infliximab administrations.

The manufacturer of romiplostim suggests that the romiplostim administrations be costed at 15 minutes of a day ward nurse including costs for qualifications using the PSSRU costings. PSSRU suggests £46 per hour and £92 per hour of direct clinical patient time. These translate into £11.50 and £23.00 per 15 minutes, with the manufacturer of romiplostim preferring the £11.50 cost. How compatible these estimates are with NHS reference costs based upon HRGs is a moot point.

Possible romiplostim administration costs

	SB12Z	Haem. OP.	PSSRU £23	PSSRU £11
1 st 4 administrations	£204.81	£147.53	£23.00	£11.50
Net vs SB12Z		-£56	-£181	-£193
Subsequent administrations	£56.54	£40.80	£6.35	£3.17
Net vs SB12Z		-£16	-£50	-£53

These have to be viewed alongside the romiplostim BNF list price of £482 for a 250-microgram vial, with more than one vial being required per administration.

3.7 Anti-D is no longer used for non-splenectomised patients

GSK sets the rate of anti-D for splenectomised patients to zero, but not for non-splenectomised patients.

Relevant multivariate sensitivity analyses were not conducted.

The following attempts to address the concerns raised by consultees and commentators on the ACD, though this does not imply that these are necessarily the most reasonable base case assumptions.

These replicate the base cases of tables 93 and 94 of the ERG report. These are then subject to both univariate and multivariate sensitivity analyses. The results of these are presented for the Appraisal Committee's preferred "alternative base case". Two tables are presented for each set of sensitivity analyses;

- one comparing eltrombopag, romiplostim and the non-TPO sequence; and,
- one comparing eltrombopag with romiplostim to draw out the relative cost effectiveness of the TPOs in isolation, given that NICE has already recommended romiplostim.

Univariate sensitivity analyses performed:

- USA01 RAISE SF-6D utilities
- USA02 anti-D removed from non-splenectomised rescue
- USA03 Odds ratio of 0.22 applied resulting in overall response¹ rates of
 - 60% for eltrombopag and 87% for romiplostim for the splenectomised
 - 72% for eltrombopag and 92% for romiplostim for the non-splenectomised
- USA04 Odds ratio of 0.15 applied resulting in overall response rates of
 - 60% for eltrombopag and 91% for romiplostim for the splenectomised
 - 72% for eltrombopag and 94% for romiplostim for the non-splenectomised
- USA05 Romiplostim vials 1.54 for splenectomised and 1.10 for non-splenectomised
- USA06 Romiplostim administration cost £147.53
- USA07 Romiplostim administration cost £23.00
- USA08 Romiplostim administration cost £11.50

Multivariate sensitivity analyses performed:

- MSA01 RAISE SF-6D utilities and anti-D removed from non-splenectomised rescue

The above combined with:

- MSA02 Odds ratio of 0.15 applied resulting in overall response rates of
 - 60% for eltrombopag and 91% for romiplostim for the splenectomised
 - 72% for eltrombopag and 94% for romiplostim for the non-splenectomised

MSA01 and MSA02 combined with:

- MSA03 Romiplostim vials 1.54 for splenectomised and 1.10 for non-splenectomised

¹ Note that the base case applies the Any Response definition with a 76% response rate for the splenectomised and an 80% response rate for the non-splenectomised.

MSA01, MSA02 and MSA03 combined with each of the following:

- MSA04 Romiplostim administration cost £147.53
- MSA05 Romiplostim administration cost £23.00
- MSA06 Romiplostim administration cost £11.50

“Alternative” base case and further univariate sensitivity analyses

Splenectomised patients

“Alternative” base case for splenectomised patients from Table 93 of the ERG report and further univariate sensitivity analyses; ICERs represent the cost per QALY of the individual TPO compared with non-TPO.

	Costs			QALYs			ICERs		
	ELTR	ROMI	Non-TPO	ELTR	ROMI	Non-TPO	ELTR	ROMI	Non-TPO
Base case	£313,050	£400,809	£278,253	14.78	14.78	14.32			
Δ vs ELTR	..	£87,758	-£34,797	..	0.00	-0.46	..	Dom.	..
Δ vs non-TPO	£34,797	£122,555	..	0.46	0.46	..	£75,297	£265,196	..
	Δ cost			Δ QALY			ICERs		
	ELTR	ROMI	Non-TPO	ELTR	ROMI	Non-TPO	ELTR	ROMI	Non-TPO
USA01 RAISE SF-6D	£34,797	£122,555	..	0.38	0.38	..	£90,753	£319,632	..
USA03 0.22 odds ratio	£27,912	£140,187	..	0.37	0.53	..	£76,195	£264,876	..
USA04 0.15 odds ratio	£27,912	£146,006	..	0.37	0.55	..	£76,195	£264,787	..
USA05 romi. dose	£34,797	£85,159	..	0.46	0.46	..	£75,297	£184,274	..
USA06 £147.53 romi. admin	£34,797	£119,147	..	0.46	0.46	..	£75,297	£257,820	..
USA07 £23.00 romi. admin	£34,797	£111,735	..	0.46	0.46	..	£75,297	£241,783	..
USA08 £11.50 romi admin	£34,797	£111,051	..	0.46	0.46	..	£75,297	£240,302	..

“Alternative” base case for splenectomised patients - cost effectiveness of TPOs; ICERs represent the cost per QALY of romiplostim compared with eltrombopag; “Dom.” indicating that romiplostim is dominated by eltrombopag

	Costs		QALYs		ICERs	
	ELTR	ROMI	ELTR	ROMI	ELTR	ROMI
Base case	£313,050	£400,809	14.78	14.78		
Δ vs ELTR		£87,758		0.00		Dom.
	Δ cost		Δ QALY		ICERs	
	ELTR	ROMI	ELTR	ROMI	ELTR	ROMI
USA01 RAISE SF-6D	..	£87,758	..	0.00	..	Dom.
USA03 0.22 odds ratio	..	£112,275	..	0.16	..	£689,084
USA04 0.15 odds ratio	..	£118,094	..	0.19	..	£638,042
USA05 romi. dose	..	£50,362	..	0.00	..	Dom.
USA06 £147.53 romi. admin	..	£84,349	..	0.00	..	Dom.
USA07 £23.00 romi. admin	..	£76,938	..	0.00	..	Dom.
USA08 £11.50 romi admin	..	£76,254	..	0.00	..	Dom.

Non-splenectomised patients

“Alternative” base case for non-splenectomised patients from Table 94 of the ERG report and further univariate sensitivity analyses; ICERs represent the cost per QALY of the individual TPO compared with non-TPO.

	Costs			QALYs			ICERs		
	ELTR	ROMI	Non-TPO	ELTR	ROMI	Non-TPO	ELTR	ROMI	Non-TPO
Base case	£230,375	£270,970	£154,845	15.10	15.10	14.39			
Δ vs ELTR	..	£40,595	-£75,531	..	0.00	-0.71	..	Dom.	..
Δ vs non-TPO	£75,531	£116,126	..	0.71	0.71	..	£106,800	£164,201	..
	Δ cost			Δ QALY			ICERs		
	ELTR	ROMI	Non-TPO	ELTR	ROMI	Non-TPO	ELTR	ROMI	Non-TPO
USA01 RAISE SF-6D	£75,531	£116,126	..	0.57	0.57	..	£133,508	£205,264	..
USA02 Anti-D removed	£81,119	£121,714	..	0.71	0.71	..	£113,560	£170,389	..
USA03 0.22 odds ratio	£68,172	£133,281	..	0.64	0.81	..	£106,893	£164,054	..
USA04 0.15 odds ratio	£68,172	£136,636	..	0.64	0.83	..	£106,893	£164,030	..
USA05 romi. dose	£75,531	£109,579	..	0.71	0.71	..	£106,800	£154,945	..
USA06 £147.53 romi. admin	£75,531	£111,133	..	0.71	0.71	..	£106,800	£157,141	..
USA07 £23.00 romi. admin	£75,531	£100,277	..	0.71	0.71	..	£106,800	£141,792	..
USA08 £11.50 romi admin	£75,531	£100,277	..	0.71	0.71	..	£106,800	£141,792	..

“Alternative” base case for non-splenectomised patients cost effectiveness of TPOs; ICERs represent the cost per QALY of romiplostim compared with eltrombopag; “Dom.” indicating that romiplostim is dominated by eltrombopag

	Costs		QALYs		ICERs	
	ELTR	ROMI	ELTR	ROMI	ELTR	ROMI
Base case	£230,375	£270,970	15.10	15.10		
Δ vs ELTR		£40,595		0.00		Dom.
	Δ cost		Δ QALY		ICERs	
	ELTR	ROMI	ELTR	ROMI	ELTR	ROMI
USA01 RAISE SF-6D	..	£40,595	..	0.00	..	Dom.
USA02 Anti-D removed	..	£40,595	..	0.00	..	Dom.
USA03 0.22 odds ratio	..	£65,109	..	0.17	..	£372,782
USA04 0.15 odds ratio	..	£68,463	..	0.20	..	£350,685
USA05 romi. dose	..	£34,048	..	0.00	..	Dom.
USA06 £147.53 romi. admin	..	£35,602	..	0.00	..	Dom.
USA07 £23.00 romi. admin	..	£24,747	..	0.00	..	Dom.
USA08 £11.50 romi admin	..	£24,747	..	0.00	..	Dom.

“Alternative” base case and further multivariate sensitivity analyses

Splenectomised patients

“Alternative” base case for splenectomised patients from Table 93 of the ERG report and further multivariate sensitivity analyses; ICERs represent the cost per QALY of the individual TPO compared with non-TPO.

	Costs			QALYs			ICERs		
	ELTR	ROMI	Non-TPO	ELTR	ROMI	Non-TPO	ELTR	ROMI	Non-TPO
Base case	£313,050	£400,809	£278,253	14.78	14.78	14.32			
Δ vs ELTR	..	£87,758	-£34,797	..	0.00	-0.46	..	Dom.	..
Δ vs non-TPO	£34,797	£122,555	..	0.46	0.46	..	£75,297	£265,196	..
	Δ cost			Δ QALY			ICERs		
	ELTR	ROMI	Non-TPO	ELTR	ROMI	Non-TPO	ELTR	ROMI	Non-TPO
MSA01 RAISE SF-6D	£34,797	£122,555	..	0.38	0.38	..	£90,753	£319,632	..
MSA02 0.15 odds ratio	£27,912	£146,006	..	0.30	0.46	..	£91,854	£319,099	..
MSA03 romi. dose	£27,912	£101,273	..	0.30	0.46	..	£91,854	£221,335	..
MSA04 £147.53 romi. admin	£27,912	£97,241	..	0.30	0.46	..	£91,854	£212,521	..
MSA05 £23.00 romi. admin	£27,912	£88,473	..	0.30	0.46	..	£91,854	£193,360	..
MSA06 £11.50 romi admin	£27,912	£87,664	..	0.30	0.46	..	£91,854	£191,591	..

“Alternative” base case for splenectomised patients - cost effectiveness of TPOs; ICERs represent the cost per QALY of romiplostim compared with eltrombopag

	Costs		QALYs		ICERs	
	ELTR	ROMI	ELTR	ROMI	ELTR	ROMI
Base case	£313,050	£400,809	14.78	14.78		
Δ vs ELTR		£87,758		0.00		Dom.
	Δ cost		Δ QALY		ICERs	
	ELTR	ROMI	ELTR	ROMI	ELTR	ROMI
MSA01 RAISE SF-6D	..	£87,758	..	0.00	..	Dom.
MSA02 0.15 odds ratio	..	£118,094	..	0.15	..	£768,427
MSA03 romi. dose	..	£73,361	..	0.15	..	£477,355
MSA04 £147.53 romi. admin	..	£69,329	..	0.15	..	£451,115
MSA05 £23.00 romi. admin	..	£60,561	..	0.15	..	£394,067
MSA06 £11.50 romi admin	..	£59,752	..	0.15	..	£388,799

Non-splenectomised patients

“Alternative” base case for non-splenectomised patients from Table 94 of the ERG report and further multivariate sensitivity analyses; ICERs represent the cost per QALY of the individual TPO compared with non-TPO.

	Costs			QALYs			ICERs		
	ELTR	ROMI	Non-TPO	ELTR	ROMI	Non-TPO	ELTR	ROMI	Non-TPO
Base case	£230,375	£270,970	£154,845	15.10	15.10	14.39			
Δ vs ELTR	..	£40,595	-£75,531	..	0.00	-0.71	..	Dom.	..
Δ vs non-TPO	£75,531	£116,126	..	0.71	0.71	..	£106,800	£164,201	..
	Δ cost			Δ QALY			ICERs		
	ELTR	ROMI	Non-TPO	ELTR	ROMI	Non-TPO	ELTR	ROMI	Non-TPO
MSA01 RAISE SF-6D	£81,119	£121,714	..	0.57	0.57	..	£141,978	£213,029	..
MSA02 0.15 odds ratio	£73,196	£143,247	..	0.52	0.67	..	£142,012	£212,964	..
MSA03 romi. dose	£73,196	£135,516	..	0.52	0.67	..	£142,012	£201,469	..
MSA04 £147.53 romi. admin	£73,196	£129,660	..	0.52	0.67	..	£142,012	£192,763	..
MSA05 £23.00 romi. admin	£73,196	£116,929	..	0.52	0.67	..	£142,012	£173,837	..
MSA06 £11.50 romi admin	£73,196	£115,753	..	0.52	0.67	..	£142,012	£172,089	..

“Alternative” base case for non-splenectomised patients - cost effectiveness of TPOs; ICERs represent the cost per QALY of romiplostim compared with eltrombopag

	Costs		QALYs		ICERs	
	ELTR	ROMI	ELTR	ROMI	ELTR	ROMI
Base case	£230,375	£270,970	15.10	15.10		
Δ vs ELTR		£40,595		0.00		Dom.
	Δ cost		Δ QALY		ICERs	
	ELTR	ROMI	ELTR	ROMI	ELTR	ROMI
MSA01 RAISE SF-6D	..	£40,595	..	0.00	..	Dom.
MSA02 0.15 odds ratio	..	£70,052	..	0.16	..	£445,574
MSA03 romi. dose	..	£62,320	..	0.16	..	£396,394
MSA04 £147.53 romi. admin	..	£56,464	..	0.16	..	£359,148
MSA05 £23.00 romi. admin	..	£43,733	..	0.16	..	£278,172
MSA06 £11.50 romi admin	..	£42,558	..	0.16	..	£270,694