Response to request for clarification regarding PFS fit

Roche Products Limited

Our apologies for the two labelling errors and missing variable values in Appendix 1 which caused the presumed "errors" in the model. These have been corrected in the text below with all changes noted in blue. These values can also be checked in the Excel model provided to NICE and the ERG. The sheets, "Lognormal", "Weibull", "Gompertz", etc. associated with each parametric function simply need to be unhidden (this can easily be changed under the Properties Window for each sheet).

GROUP	Parametric distribution	Paramenters supplied in Appendix 1	Expected parameters	Comment
FC	Exponential	Lambda 0.021538853	Lambda	Supplied as expected
FC-R	Exponential	Lambda 0.032648063	Lambda	
FC	Lognormal	Lambda (mu) 3.03372945 Gamma (sigma) 1.26999224	Mu & sigma	Three parameters supplied; two given same label; one parameter (0.0190891349) does not make sense – this belongs to the Weibull parameter but was inappropriately labelled
FC-R	Lognormal	Lambda (mu) 3.43910477 Gamma (sigma) 1.26999224	Mu & sigma	Only one parameter supplied. Useless. – inappropriately labelled - it was provided under the label log logistic previously.
FC	Weibull	Gamma (shape) 1.168851232 Lambda (scale) 0.019089139	Shape & scale parameters	Gamma value is identical for FC and FC-R to 9 decimal places. Only one parameter supplied for FC - it was provided in the appendix but inappropriately labelled lognormal.
FC-R	Weibull	Gamma (shape) 1.168851232 Lambda (scale) 0.012247453	Shape & scale parameters	
FC	Loglogistic	Lambda (scale) 0.012562418 Gamma (shape) 1.439731176	Shape & scale parameters	Supplied as expected
FC-R	Loglogistic	Lambda (scale) 0.007234917 Gamma (shape) 1.439731176	Shape & scale parameters	The gamma parameter is the same as that provided above for lognormal FC. Correct value provided.
FC	Gompertz	Lambda (scale) 0.028526053 Gamma (shape) 0.009632453	Shape & scale parameters	The gamma value is identical for FC and FC-R to 9 decimal places.
FC-R	Gompertz	Lambda (scale) 0.018423665 Gamma (shape) 0.009632453	Shape & scale parameters	
FC	Gamma	*	Parameters for generalised gamma distribution	
FC-R	Gamma			

* In view of the errors noted and the large number of parameters for the gamma distribution listed by the manufacturer and the general lack of clarity the ERG have not extracted these values.

It appears that the ERG has misunderstood the nature of these parametric models in their assumption that the identical gamma values for R-FC and FC also represents an error. It is expected that the gamma values are identical for R-FC and FC for the Weibull, Log logistic, Gamma and Gompertz parametric models under the assumption proportional hazard. These represent single models with the ancillary parameter (gamma or shape) left the same.

For completeness, we have provided the parameters for the Gamma distribution below, taken directly from the associated sheet entitled “Gamma” of the Excel model. The origin of each of these values can be further inspected by the ERG by reviewing the formulas on this sheet:

	FC		R-FC
Lambda	0.126698583	**Lambda**	0.093024002
Gamma	1.750663612	**Gamma**	1.750663612
Delta	0.793629277	**Delta**	0.793629277

As these parameter values have now been clarified, Roche strongly feels that the ERG is not justified in its rationale for requesting the clinical trial patient-level data for the purpose of re-assessing the PFS parametric fit. We believe this for the following reasons: firstly, each parametric fit was overlaid on the Kaplan-Meier PFS curve and was provided in the original submission in Figure 25. Therefore the fit can be assessed by visual inspection. Furthermore, the goodness of fit of each parametric function for PFS was provided in the original submission in Table 61.