

Attachment to End Point – Total Symptom Score during CPTs

Primary analysis

Within the MCP-mod procedure, three candidate models were investigated for dose-response characterization: the Emax, the linear in log and the logistic model. Based on the Akaike Information Criterion (AIC), the linear in log model showed the best fit to the observed dose response data; and was assigned the highest weight in the model averaging procedure. Modeling results were fairly consistent between the three candidate models. The final model was determined using model averaging.

Table: MCP-Mod analysis – tabular results – modified Full Analysis Set

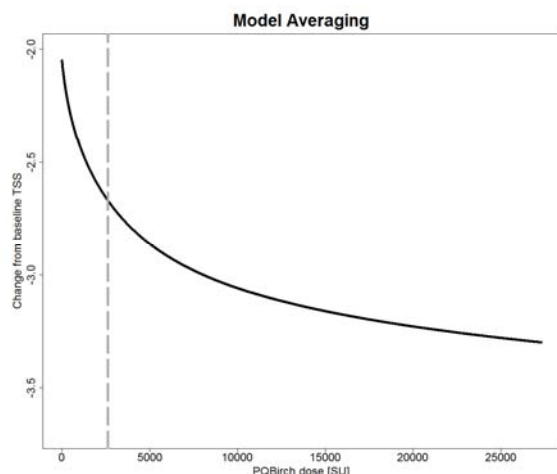
Multiple contrasts procedure step		
Model	t Statistic	Adjusted p-value
Emax	2.821	0.0044
Linear in log	2.893	0.0034
Logistic	2.676	0.0068

Modelling step			
Model	AIC	Normalized weight for model averaging	ED50 [SU]
Emax	1181.4	0.2355	2915.7
Linear in log-dose	1179.2	0.6887	2470.6
Logistic	1183.7	0.0758	2923.0
Model averaging			2609.7

AIC: Akaike Information Criterion, smaller values indicate better model fit;

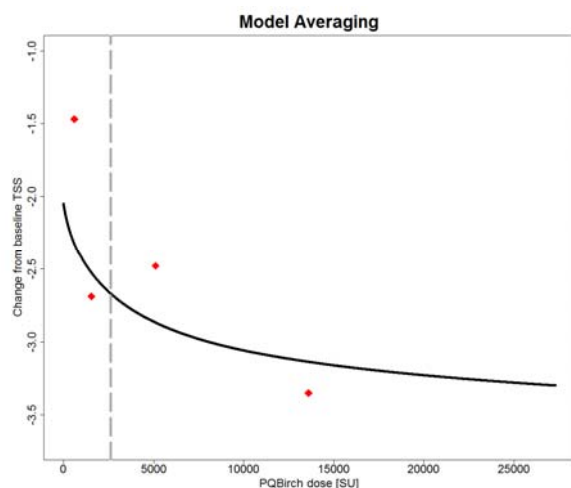
ED50: The minimal dose that achieves 50% of the maximum achievable TSS change from baseline compared to placebo

Graphical display: MCP-Mod analysis – final results – modified Full Analysis Set (primary analysis), dashed line represents the ED50



The highest dose regimen 27,300 SU was approaching the plateau of dose response curve. The appearance of the dose regimen response curve rising to a plateau is similar to that which has been seen in earlier studies as part of Market approval.

Graphical display: MCP-Mod analysis – final results including point estimates from the 4 dose groups of PQBirch 203 study (EudraCT number is 2012-004336-28) – modified Full Analysis Set (primary analysis)



Providing assurance to the selection of the dose regimen to enter the phase III study, there appears a consistency of the results of the earlier PQBirch203 dose response study and the PQBirch204. The point estimates of PQBirch203 lie closely to the estimated curve for PQBirch204.