Randomised controlled trials define shape of dose-response for Pollinex Quattro Birch allergoid immunotherapy

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On-line Supporting Information: description of methods; figures and legends

Appendix 1

Statistical methods MCP-Mod

The MCP-Mod is a 2-step statistical procedure, which ensures that the pre-defined significance level (in most cases 5.0 %) is not increased for the complete statistical analysis. As a consequence, the conclusions drawn from the procedures can be accepted under the error probability of 5 %.

The first step, the multiple comparison step, compares the different dose groups of a study using several dose-response models that need to be pre-selected.

A dose-response model is a functional relation between the dose of a drug and the response. The easiest model is a linear model, which can be fully described by 2 parameters: the slope of the line, and the intersection point of the line with the y-axis. Other examples for such functional relation are the E_{max}-function, the linear-in-log function, and the logarithmic function. Similar to a linear relation, the exact form of the functional relation can be fully described by 1 or 2 parameters.

The multiple comparison step tests whether any dose-response can be detected using the different pre-specified candidate models. The test procedure provides a p-value for each candidate model. The p-value is equal to the probability that any dose-response for the candidate model is a by-chance finding. The statistical test procedure is constructed in a way that p-values are adjusted for multiplicity, which means that the overall error probability of 5% is maintained, although a number of tests are performed.

The second step in MCP-Mod is the modelling step. It is performed only in those cases in which the dose-response could be shown with the statistical test, i.e. if the first step could be completed successfully.

In order to determine the final model for the given data, it is possible to either select the best candidate model or to create a dose-response model that uses all significant candidate models at the same time. The latter is called model averaging. The selection of a model or the building of the average model relies on criteria that evaluate the deviation of the observed data (i.e. the dose response observed for each dose that was investigated) from the theoretical model. The closer the observed data is to the theoretical model (the better the 'fit') the higher weight this model gets in the model averaging step.

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With the selection of 1 model or calculation of the average model, 1 curve is presented, which estimates the relation between the response and the dose of the product over the whole range of doses that were included in the study.

The response of a dose that was not tested in the study but is higher than the lowest dose tested and smaller than the highest dose tested, can be estimated from the final model.

Appendix 2

Conjunctival provocation test (CPT) – Method (Pfaar et al reference 36**)**

A CPT instruction guide, preparation sheet and data collection form were provided and followed during the study. CPT was only conducted on subjects with no visible and/or reported eye symptoms or complaints on the day of the assessment. No contact lenses were worn on the day of the CPT prior to the procedure.

The following CPT concentrations were available for testing at Visit 1 (or Visit 1a) and Visit 2 (and Visit 2a if applicable): 0.3, 1.0, 3.0 and 10 HEP/mL. In addition, the original reconstituted allergen solution with a concentration of 30 HEP/mL was available for use at Visit 8, if required. Reconstitution was performed by drawing 4.8 mL from a vial with 5.0 ± 0.2 mL of solvent and dispensing into a vial with lyophilised birch extract. Further dilution steps were detailed in the CPT instruction manual and preparation sheet. Aqueous diluent served as negative control.

During the screening CPT at Visit 1 or 1a, initially 1 drop of diluent (negative control) was administered to the right eye, which was the reference eye during CPT. After 10 minutes, 4 symptoms (eye redness, tearing, itching and irritation) were scored for the reference eye by the investigator in conjunction with the subject on a scale of 0 to 3 points (0 = absent; 1 = mild; 2 = moderate; 3 = severe). The reference eye was assessed only once and needed to achieve a TSS of ≤3 to be considered valid and to allow the subject to continue in the study. Following achievement of a valid negative control result, 1 drop of the lowest available birch allergen extract (0.3 HEP/mL) was administered in the lower conjunctival sac of the left eye and assessed after 10 minutes. This procedure was repeated with increasing concentrations of birch allergen extract until a TSS of ≥6 after adjustment for reference eye score (i.e. test eye TSS - reference eye TSS ≥6) had been reached. The concentration and TSS score were recorded and constituted the screening TSS. In the event that no positive test was achieved after application of all available CPT concentrations, the subject was discontinued from the study.

The CPT at Visit 2 again started with 1 drop of diluent in the right eye and, pending a valid result at the evaluation after 10 minutes, 1 drop of birch allergen extract at the concentration eliciting a positive CPT at Visit 1 or 1a was administered in the left eye. Allergen extracts at lower concentrations than this, which had previously elicited a positive response, were not tested. If the CPT was once again positive (i.e. TSS ≥6, adjusted for reference eye score) after 10 minutes, the score was recorded as the Baseline TSS and the subject was randomised. If the CPT was negative, higher allergen concentrations were administered at increasing strengths according to procedure until a TSS ≥6, adjusted for reference eye score, was achieved. This higher concentration had to be confirmed at a second confirmatory CPT visit (Visit 2a) within 6-8 days of Visit 2 to obtain the Baseline TSS and for the subject to progress to the randomisation procedure. If no positive test was achieved at Visit 2 after application of all available allergen concentrations (up to 10 HEP/mL) or the confirmatory test at Visit 2a was negative, the subject was discontinued.

During Visit 8 the CPT was conducted by applying 1 drop of diluent to the right eye and following evaluation after 10 minutes, 1 drop of birch allergen extract at the concentration eliciting the positive response at the confirmatory CPT (Visit 2 or 2a). Allergen extracts of lower concentrations were not tested. After 10 minutes, the TSS was recorded and if found to be < 6 after adjustment for reference eye score, higher allergen concentrations were administered at increasing strengths according to procedure, until a TSS of ≥6 was reached after adjustment for reference eye score.

CPT was not stopped until a positive test was achieved, or no further concentrations were available for testing. At the end of each CPT, a suitable relief medication was administered to relieve remaining eye symptoms, if necessary.

On-line Figures and Legends

Figure 1: Box plots of IgG, IgG4 and IgE plus IgG4/IgE ratio in PQBirch203 study

Legend:

The individual results for each cumulative dose showing values for IgE, IgG, IgG4 and IgG4/IgE ratio measured at screening and 3-4 weeks after completion of treatment in the PQBirch203 study each cumulative dose is shown a shaded grey. lower line of box = 1st quartile, line inside box = median, upper line of box = 3rd quartile, + = mean, circle = values below/upper 1.5 * (3rd quartile - 1st quartile), lower/upper whisker = minimum/maximum value above/below 1.5 * (3rd quartile - 1st quartile)

Figure 1a: Box plot for IgE [kU/L] - Modified Full Analysis Set

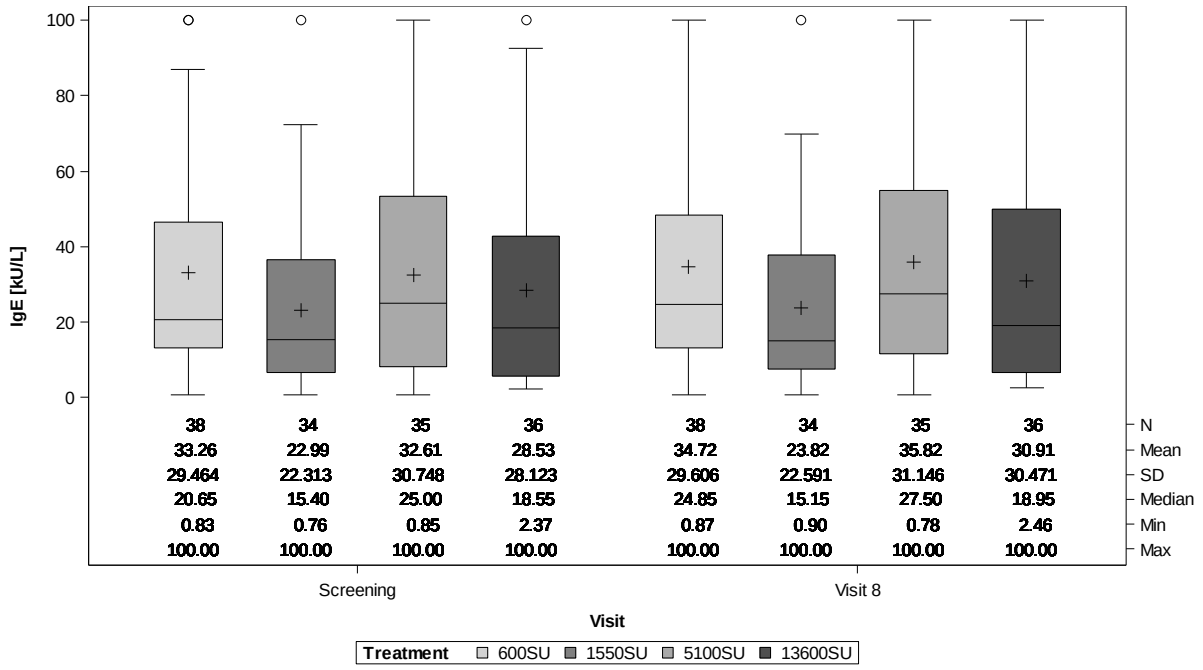


Figure 1b: Box plot for IgG [kU/L] - Modified Full Analysis Set

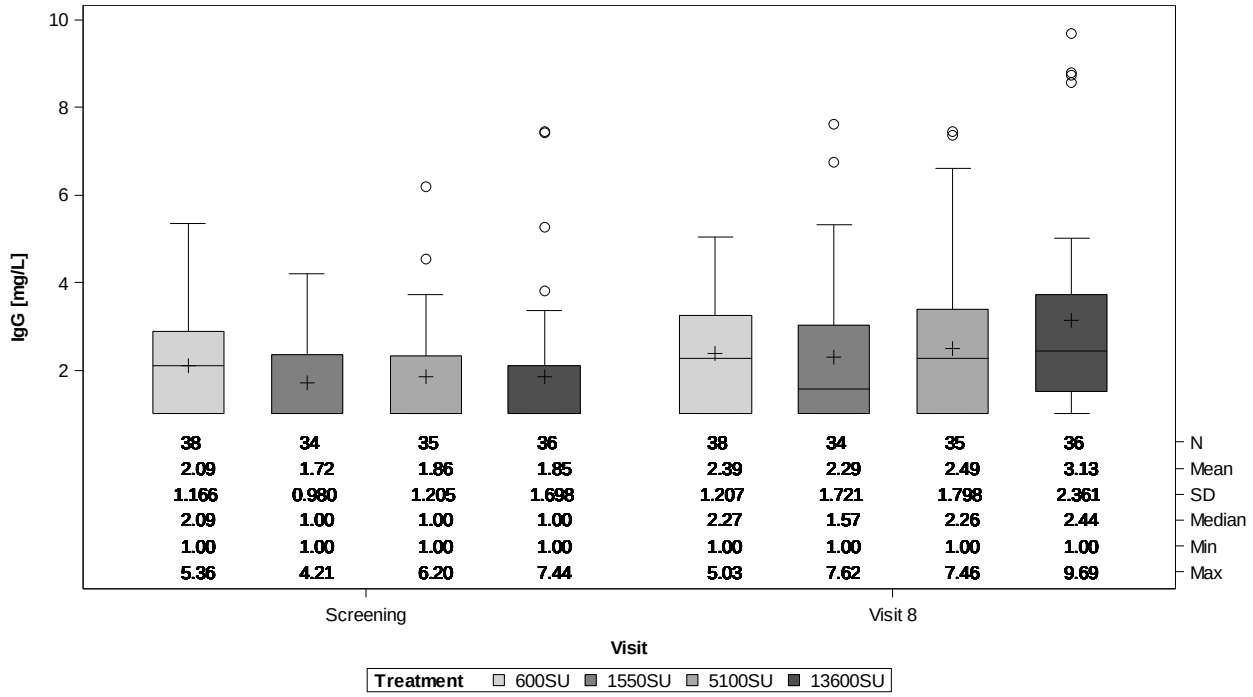


Figure 1c: Box plot for IgG4 [mg/L] - Modified Full Analysis Set

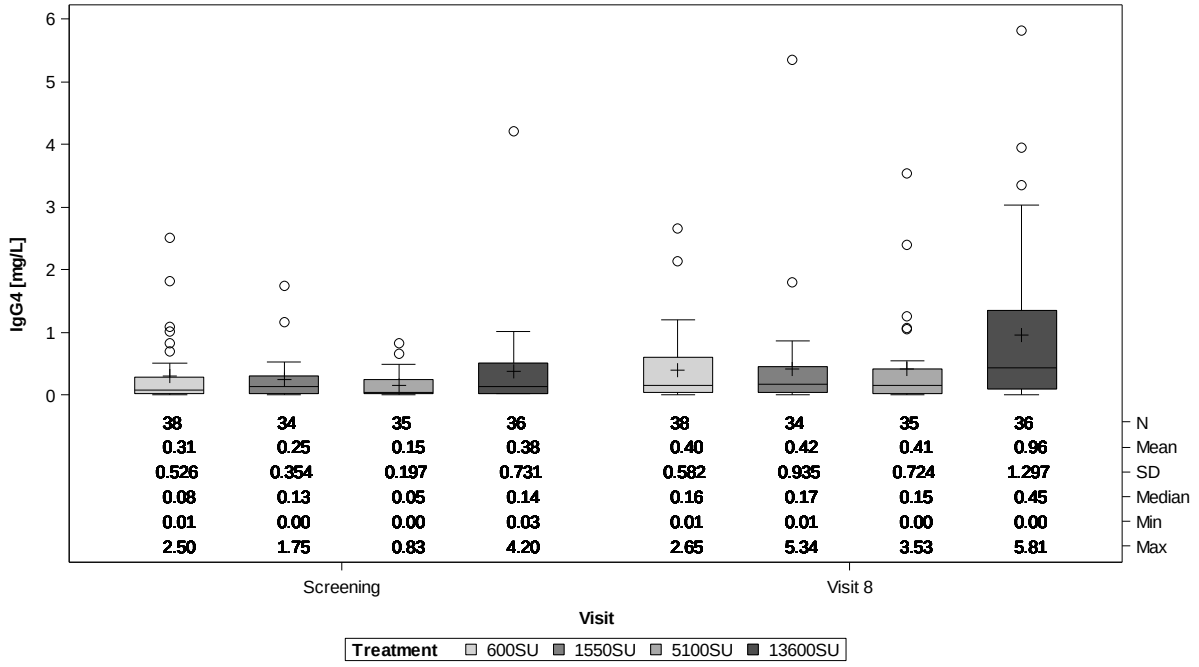


Figure 1d: Box plot for IgG4/IgE [%] – Modified Full Analysis Set

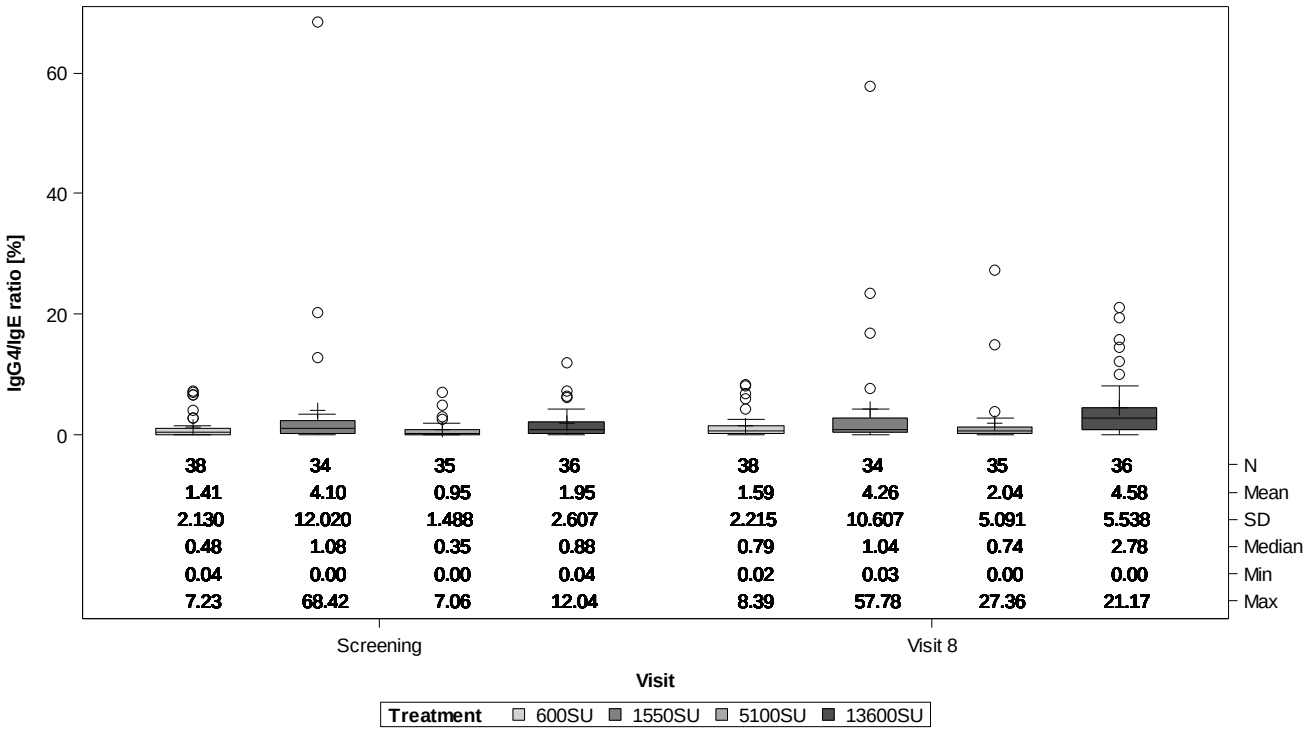
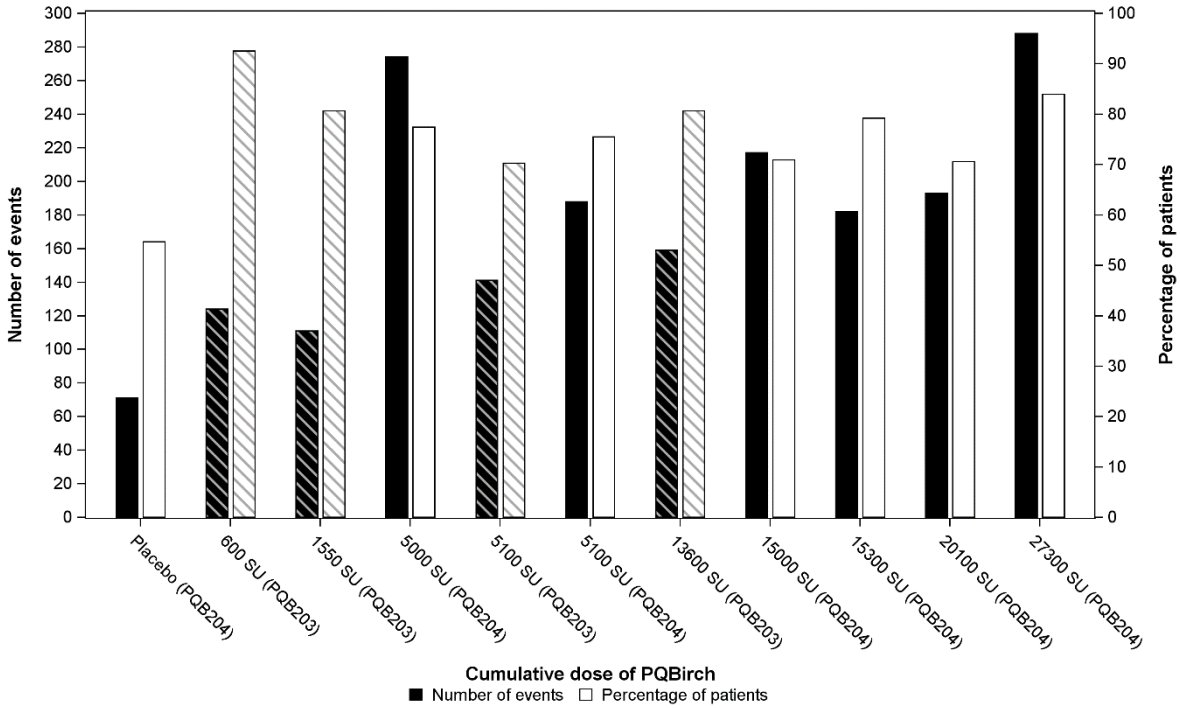
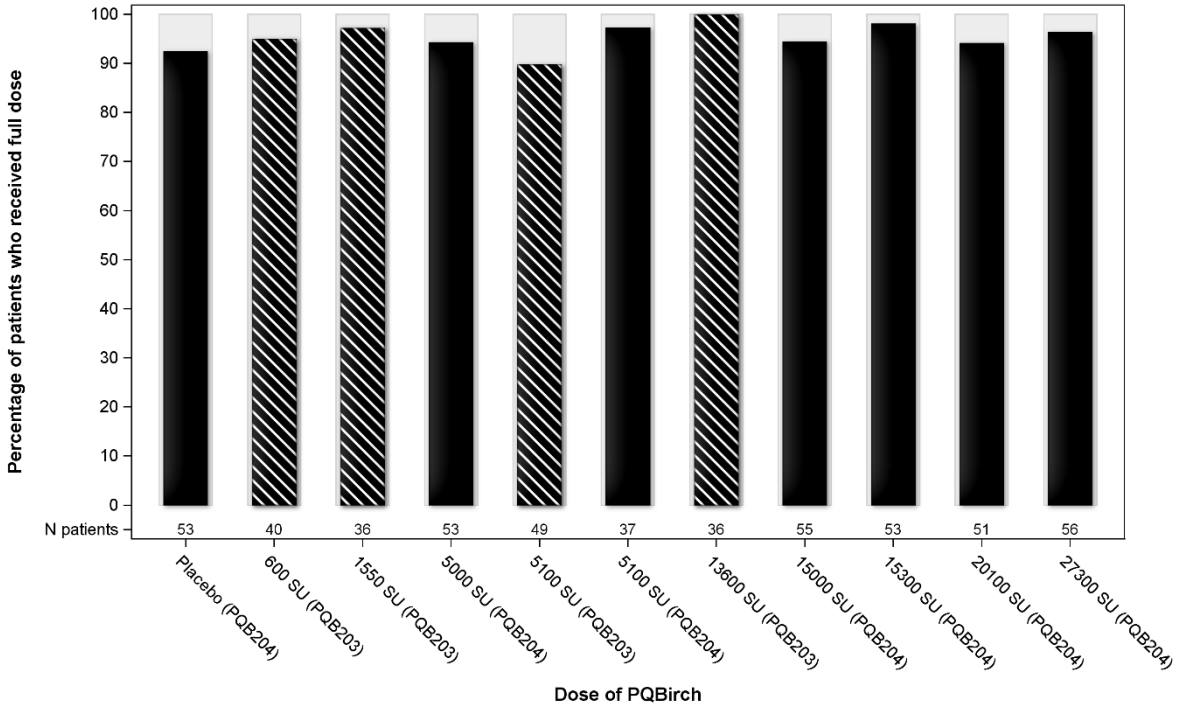


Figure 2: Treatment-emergent adverse events per injected dose of PQ Birch



Legend:
Number of treatment-emergent adverse events (TEAEs) and percentage of patients experiencing TEAEs for each cumulative dose of PQ Birch and placebo in the PQBirch203 and PQBirch204 studies. Dashed columns represent the PQBirch203 study and undashed columns represent the PQBirch204 study. SU: standardised unit

Figure 3: Compliance: Number of Subjects who received all 6 scheduled injections (Safety Set)



Legend:
The compliance for each cumulative dose from the PQBirch203 and 204 as the percentage of subjects who received all 6 scheduled injections. Dashed columns represent the PQBirch204 study and solid columns represent the PQBirch203 study. SU: standardised units.