Statistical analysis

For data analysis Statistical Package for Social Sciences (SPSS®, Chicago, IL) for Windows, version 23.0 was used. Normal distribution of all dependent variables was checked using Shapiro-Wilk analysis (for samples <50 participants) or Kolmogorov-Smirnov analysis (for samples >50 participants). Chi-square test was used for the comparison of percentages, whereas means were compared with the use of independent samples *t*-test or Mann-Whitney *U* test for non-parametric data. Two-tailed levels of significance were used in all statistical calculations. One-way ANOVA or Kruskal-Wallis analysis was used for the comparison of means of dependent continuous variables when data were divided in ≥3 groups. To evaluate the relationship among different parameters we used a multivariate Cox regression model analysis. Correlation analyses were performed with Pearson product-moment correlation coefficient or Spearman's Rank Order Correlation for non-parametric data. Putative baseline predictors of a change in the level of HA and HYAL-1 after moderate or severe exacerbations were assessed using linear mixed-effects models. This exploratory analysis was performed using the R statistical software version 3.4.2 with the extension package 'lme4'.