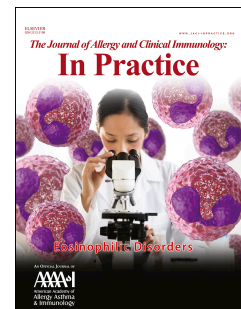


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Variability in Blood Eosinophil Counts in Patients with Eosinophilic Asthma

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22

23 **Declaration of interest:**

24 Jonathan Corren has served as a consultant for Genentech, AstraZeneca, Novartis,
25 Regeneron and Sanofi, has served on speakers' bureaus for Genentech and
26 AstraZeneca, and his institution has received research grants from Genentech,
27 Regeneron and Sanofi. Evelyn Du is an employee of Teva Pharmaceuticals.
28 Rebecca Vanlandingham is a former employee of Teva Pharmaceuticals. Ananda
29 Gubbi is an employee of Kelly OGC who has served as a consultant for Teva
30 Pharmaceuticals.

31

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Abstract

Background: Blood eosinophil (EOS) counts are critical to the accurate identification of asthma phenotypes. However, there are few long-term data on intra-individual EOS count variability among patients with eosinophilic asthma.

Objective: This *post hoc* analysis of two phase III clinical trials from the reslizumab BREATH program explored the variability of blood EOS counts in patients with eosinophilic asthma receiving placebo.

Methods: Pooled data from study participants receiving placebo (previously randomized 1:1 to receive reslizumab or placebo) were analyzed for blood EOS count variability over 52 weeks. EOS counts were measured up to twice during screening, every 4 weeks from randomization to the end of treatment and at the 90-day follow-up visit.

Results: Of 476 included patients, 31 (6.5%), 38 (8.0%), 55 (11.6%) and 352 (73.9%) patients had baseline blood EOS counts of <150 cells/ μ L, $\geq$ 150 to <300 cells/ μ L, $\geq$ 300 to <400 cells/ μ L and $\geq$ 400 cells/ μ L, respectively. Patients frequently shifted between EOS count categories during the 52-week treatment period, most often moving to the highest EOS category. Among patients in each of the lower three EOS categories, 27 to 56% of patients shifted to the $\geq$ 400 cells/ μ L category at some point during the treatment period.

Conclusion: Intra-individual variability in blood EOS count was high among eosinophilic asthma patients receiving placebo, with shifts to $\geq$ 400 cells/ μ L from lower categories frequently observed. Repeat determinations of blood EOS count may be important to ensure appropriate selection of therapy in patients with severe asthma.

Clinical Trial Registration: NCT01287039 and NCT01285323**Highlights Box**

What is already known about this topic? Blood eosinophil counts are key to diagnosis and monitoring of eosinophilic asthma.

What does this article add to our knowledge? Patients' blood eosinophil counts vary substantially over time, and rapid shifts from low to high EOS counts are not uncommon.

How does this study impact current management guidelines? Repeated blood eosinophil count measurements may benefit the evaluation and management of symptomatic asthma patients.

Keywords: Eosinophils, EOS, variability, eosinophilia, asthma, reslizumab, placebo

Abbreviations

CI	Confidence interval
EOS	Eosinophil(s)
ICS	Inhaled corticosteroids
IgG4	Immunoglobulin G4
IL-5	Interleukin 5
IV	Intravenous
LABA	Long-acting beta ₂ agonist
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonist
mAb	Monoclonal antibody
OCS	Oral corticosteroids
SCS	Systemic corticosteroids

84 SE Standard error

Introduction

Eosinophilic asthma is a type of asthma characterized by elevated eosinophil (EOS) counts.¹ Patients with severe eosinophilic asthma tend to have impaired lung function, poor symptom control, and are at increased risk of severe asthma exacerbations.² The maintenance and activation of EOS is dependent on interleukin 5 (IL-5), the prototypical EOS viability enhancing factor.³ Several monoclonal antibodies (mAbs) that target the IL-5 pathway (i.e., benralizumab, mepolizumab and reslizumab) are approved as add-on maintenance treatment for inadequately controlled severe eosinophilic asthma. The blood EOS count is a readily available key to the diagnosis and monitoring of eosinophilic asthma.

In clinical trials of agents that target the IL-5 pathway, a single blood EOS count is frequently applied as a biomarker to identify patients with eosinophilic asthma and as an inclusion criterion for study entry.⁴ Individuals' blood EOS counts are known to fluctuate and this intra-individual variability in blood EOS count may have implications both in clinical research and practice. The placebo arms of clinical trials in patients with eosinophilic asthma provide an opportunity to advance our understanding of the intra-individual variability of blood EOS count. However, despite this, few published long-term data exist on intra-individual EOS variability in patients with eosinophilic asthma.^{5,6}

Reslizumab is an immunoglobulin G4 (IgG4)-kappa humanized mAb that targets IL-5, thereby disrupting the maturation, activation and survival of EOS.⁷ In two duplicate, 52-week phase III clinical trials from the BREATH program, intravenous (IV) reslizumab significantly reduced the risk of asthma exacerbations, and improved

110 asthma control, lung function and quality of life in patients with inadequately
111 controlled eosinophilic asthma and a history of asthma exacerbations.⁸ The placebo
112 arms of these two phase III clinical trials from the BREATH program comprise a
113 large, prospectively-followed cohort of patients with multiple measurements of EOS
114 count over a 52-week period. The data generated from these studies were sufficient
115 to conduct a *post hoc* analysis exploring the intra-individual variability in blood EOS
116 count across several EOS count categories in patients who received placebo. We
117 hypothesized that substantial variability in EOS count would be observed over time
118 in a population of patients with eosinophilic asthma with data at multiple timepoints.

Methods

Study design and patients

The two duplicate phase III studies (NCT01287039 and NCT01285323),⁸ performed at 232 centers in Asia, Australia, North America, South America, South Africa and Europe, enrolled patients aged 12 to 75 years whose asthma was inadequately controlled at baseline (Asthma Control Questionnaire-7 score ≥ 1.5), and who had ≥ 1 exacerbation in the previous year. To be eligible, patients were required to have blood EOS count of ≥ 400 cells/ μ L as assessed within a screening period of duration ≤ 4 weeks. At baseline, all patients were taking at least a medium dose of inhaled corticosteroids (ICS; fluticasone propionate ≥ 440 μ g/day or equivalent) with or without another controller drug, which could include oral corticosteroids (OCS; ≤ 10 mg/day of prednisone or equivalent).

Patients were randomized (1:1) to receive IV reslizumab (3.0 mg/kg) or matching placebo every 4 weeks for 52 weeks, and continued their usual asthma treatment without change throughout the screening and treatment periods.

Blood EOS counts could be measured up to twice during screening to meet the inclusion criteria of blood EOS count of ≥ 400 cells/ μ L. Blood EOS were measured at the day of randomization visit (considered baseline for the current analysis) and at visits every 4 weeks from day of randomization to the end of treatment and at the 90-day follow-up visit. For each week and overall change in EOS counts, data were analyzed using a mixed effect model for repeat measurements (MMRM) with treatment, study visit, treatment by visit interaction, region, and OCS use at

enrollment as fixed factors, and covariates for height and baseline value.

Unstructured covariance structure was assumed for the repeated measures.

Current analysis

For this *post hoc* analysis, pooled data from participants in the placebo arms were analyzed for variability in blood EOS count over the 52-week treatment period.

Baseline blood EOS value was the last observed measurement prior to the first dose of placebo (i.e. blood EOS count measured on the day of randomization). Previous visit refers to the blood EOS count observed during the prior visit. Patients were categorized into four groups according to their baseline blood EOS count: <150 cells/ μ L, $\geq$ 150 to <300 cells/ μ L, $\geq$ 300 to <400 cells/ μ L and $\geq$ 400 cells/ μ L. Proportions of patients staying in the same category or shifting to different categories from baseline as well as from previous visits were analyzed at Weeks 4, 16 and 52 of the treatment period. In addition, the proportions of patients among each baseline EOS count category with post-baseline eosinophil count <150 cells/ μ L during the 52-week treatment period were analyzed. The lower threshold (150 cells/ μ L) explored in this analysis represents the lowest threshold for the definition of eosinophilia described in clinical studies of biologics for severe eosinophilic asthma.⁹

Maintenance OCS use was defined according to the presence in the electronic case report form of a coded medication class of “corticosteroids for systemic use” with route of administration “oral” on the day of randomization.

To further quantify intra-individual variability, the coefficient of variation (CV) of observed measurements over time within each patient was calculated and

summarized with mean, median and quartiles. The intra-patient CV assesses the within-patient variation relative to patient's mean EOS value. Furthermore, to explore inter- and intra-patient variabilities and the intra-patient variability relative to the total variability, a simple MMRM with study visits as fixed effects and patient as a random effect was employed. The intra-class (patient) correlation (ICC) is derived as the variability explained by the "patient" effect, also regarded as the inter-patient variability, divided by the total variability. ICC measures the strength of correlation among measurements within the same patient with higher ICC value indicating higher similarity among within-patient measurements. As with a regular correlation coefficient, an ICC < 0.3 is considered a very weak correlation; an ICC between 0.3 and 0.5 a weak correlation; an ICC between 0.5 and 0.7 a moderate correlation, and ICC > 0.7 a strong correlation. The proportion of the total variability accounted for by the intra-patient variability was also estimated as: $(1-ICC) \times 100\%$.

Finally, summary statistics (mean, median, 1st and 3rd quartiles, minimum and maximum) for absolute and percentage changes in blood EOS count from baseline and from the previous visit were calculated and presented in box plots by visit to show the magnitudes of these changes in the patient population as a whole.

Results

Patients

The pooled analysis included 476 patients who received placebo. Of these, 31 (6.5%), 38 (8.0%), 55 (11.6%) and 352 (73.9%) patients had baseline blood EOS counts of <150 cells/ μ L, $\geq$ 150 to <300 cells/ μ L, $\geq$ 300 to <400 cells/ μ L and $\geq$ 400 cells/ μ L, respectively. Baseline demographic and clinical characteristics of the placebo patients, including mean (standard error [SE]) overall EOS count at baseline, are shown in **Table I**. Of the 476 patients with an EOS count of $\geq$ 400 cells/ μ L measured during the screening period, 124 (26.1%) had an EOS count below this threshold at baseline (last measurement prior to first dose of placebo). Across the four baseline EOS count categories, the proportion of patients using maintenance OCS was greatest among those who had EOS <150 cells/ μ L at baseline (23%). The proportions of patients using maintenance OCS in the other categories were all lower (14–20%), but in combination represented 90% (66/73) of the OCS users among our population.

Intra-individual variability in EOS count was first investigated by exploring shifts between the four EOS count categories in individual patients from baseline after 4, 16 and 52 weeks of placebo treatment (**Figure 1**). Patients with baseline EOS count $\geq$ 400 cells/ μ L were by far the most likely to remain in the same EOS count category; however, even among this subset a proportion of patients – ranging from 25% at Week 4 to 31% at Week 52 – shifted to a lower EOS count category at each assessed timepoint (**Figure 1A, Table E1**). Furthermore, shifts to the highest category occurred very frequently among patients in the lower three baseline EOS categories. At Week 4, 44–55% of the patients who were in each of the three lower

categories at baseline were found to have blood EOS ≥ 400 cells/ μ L. At Week 16, 37–41% had blood EOS of ≥ 400 , and at Week 52 27–56% did so. The proportion of patients who shifted from a lower baseline EOS category to the highest EOS category did not differ greatly between groups (i.e., similar proportions of patients in each of the 3 lower categories moved to the highest category at each visit). Similarly, when shifts from one 4-weekly visit to the next were explored, fluctuations in EOS count were observed to occur at consistently high levels throughout the 52-week treatment period, such that the proportions of patients who shifted between categories at 4-weekly intervals, compared with the previous visit, were broadly similar for each timepoint (**Figure 1B, Table E2**). Similar to the results of the analysis of shifts from baseline, patients with baseline levels ≥ 400 tended to remain in the same category from visit to visit, whereas patients with baseline values < 400 had a high proportion of shifts to the highest EOS category (29.5–55.3%) from one visit to the next.

Sensitivity Analysis

Findings of a sensitivity analysis conducted in the subsets of patients who did and did not receive rescue systemic corticosteroids (SCS) during the treatment period showed that shifts from baseline EOS count category occurred both in patients who received rescue systemic corticosteroids (SCS) for acute asthma during the 52-week treatment period (n=257) and in those who did not receive rescue SCS (n=219) (**Figure E1**).

The mean intra-patient CV of measurements over time was 47.3% (median = 43.8%, 1st quartile = 32.2%, 3rd quartile = 56.0%, respectively) . While a CV $> 100\%$ is

generally considered large, CVs from repeated laboratory measurements are usually small ($<10\%$). The summaries of within-patient CVs showed that in relation to the patients' mean EOS levels, the EOS measurement values displayed moderately large fluctuations over time. The ICC for all patients was estimated by MMRM analysis as 0.475, indicated a weak to moderate correlation among patients' measurements over time. It was then estimated that approximately 52.5% of the total variability over time in blood EOS counts among the placebo group was accounted for by intra-patient variability, as opposed to differences in patient characteristics across the study population (i.e., inter-patient variability), showing that EOS counts are highly variable over time within the same patient.

Intra-individual variability analysis according to rescue systemic corticosteroid use during the treatment period

The MMRM analysis was conducted for the subsets of placebo patients who did (n=257) and did not (n=219) receive rescue SCS during the treatment period. Among patients who received rescue SCS, the ICC was estimated as 0.450 and proportion of total blood EOS variability over time accounted for by intra-patient variability as 55.0%. Among those who did not receive rescue SCS, estimated ICC was 0.523 and intra-patient variability was estimated to account for 47.7% of total variability. Hence, intra-patient correlation was observed to be slightly numerically greater among those who did not use rescue SCS than among those who did, and patients with rescue SCS use showed numerically slightly greater variability in their EOS measurements over time. However, both groups would be considered to have a weak correlation between within-patient measurements.

260

261 *Patients with post-baseline blood eosinophil count <150 cells/ μ L*

262 Proportions of patients with post-baseline blood EOS count <150 cells/ μ L at each
263 4-weekly timepoint over 52 weeks during the treatment period are shown in **Figure 2**.
264 The proportion of patients with blood EOS <150 cells/ μ L at each post-baseline
265 timepoint was highest among those with baseline EOS count <150 cells/ μ L. However,
266 of those patients who had blood EOS <150 cells/ μ L at baseline, less than 50% had
267 such a low EOS level at any post-baseline timepoint. At one timepoint (Week 28),
268 only 23.1% of these patients had EOS <150 cells/ μ L. Conversely, of the patients in
269 the highest baseline category (≥ 400 cells/ μ L), between 4.8 and 9.8% had blood EOS
270 levels <150 cells/ μ L at any post-baseline timepoint.

271 *Mean and median absolute changes in blood EOS count*

272 The absolute blood EOS count at baseline decreased during the 52-week treatment
273 period in this population of patients receiving placebo (**Figure 3**). At baseline, the
274 mean $\pm$ SE blood EOS count was 655 ± 29 cells/ μ L. Mean $\pm$ SE decreases from
275 baseline were -119 ± 26 cells/ μ L at Week 16 and -117 ± 31 cells/ μ L at Week 52
276 (**Figure 3A**). Mean and median changes in EOS count from one 4-weekly clinic visit
277 to the next were modest; however, substantial ranges of increased and decreased
278 EOS count from the previous visit were observed throughout the 52 weeks (**Figure**
279 **3B**).

280

281 *Mean and median percentage changes in blood EOS count at consecutive visits*

282 Mean and median percentage changes in EOS count from baseline fluctuated over
283 52 weeks (**Figure 4A**). Mean percentage changes in EOS count from the previous
284 visit also fluctuated somewhat while median percentage changes from previous visit

were fairly stable over 52 weeks (**Figure 4B**). Mean percentage changes from baseline ranged from 0.9 to 25.3% and from the previous visit ranged from 14.2 to 28.5%. Median percentage changes from baseline ranged from –16.7 to –6.5%, while median percentage change from the previous visit was approximately 0% for each visit (**Figure 4**). Of note, the mean percentage changes were typically much greater than the median percentage changes, since percentage changes were right-skewed as increases had no upper limit but decreases were bounded by –100.

Sensitivity Analysis

Findings of sensitivity analyses conducted in the subsets of patients who did and did not receive rescue SCS during the treatment period, exploring absolute and percentage changes, respectively, are shown in **Figures E2 and E3**. In general, these subgroups showed a similar pattern to the overall population (**Figures 3 and 4**).

Discussion

The blood EOS count serves as a very important biomarker in determining the inflammatory phenotype of patients with asthma, and optimal use of this test requires an adequate understanding of its intra-individual variability over time. Previously published long-term data for the variability of blood EOS counts in patients with eosinophilic asthma are limited. The current *post hoc* analysis of a large cohort of patients with eosinophilic asthma who received placebo in two phase III clinical trials presents long-term data with multiple timepoints for up to 52 weeks. High intra-individual variability in blood EOS count was observed in this population who received placebo in addition to their usual asthma treatment. We employed a blood EOS count of 400 cells/ μ L to define an eosinophilic phenotype. All patients included in the analysis had to have at least one screening EOS value ≥ 400 cells/ μ L to be included in the parent studies. Hence, this analysis may be most relevant to reslizumab.

Our analysis builds upon earlier investigations by including a large number of timepoints per patient and additional categories of EOS counts to facilitate a richer understanding of substantial variability in EOS counts over time in asthma patients. Our findings are consistent with both the analysis of placebo patients in lebrikizumab⁶ and the real-world findings from a clinic that treated patients with severe asthma over a 5-year period.⁵ The latter, a recent retrospective review, investigated the variability of EOS count in patients from an urban asthma clinic (N = 219) who had at least 2 EOS counts (average of 7 counts) in the 5 years prior to an index clinic visit. Of these patients, 47% had counts above and below 300 cells/ μ L during the analysis timeframe.⁵ Of note, this clinic-based population differed from the

population in the current analysis in several respects, including older patient age, higher percentage of female patients, lower percentage of patients on maintenance OCS, higher average percent predicted FEV₁, and lower mean blood EOS counts, suggesting that variability in blood EOS count may be found across subpopulations of asthmatics. Recent *post hoc* analyses of placebo arm data (N = 813) from phase IIb and phase III studies of the experimental anti-IL13 biologic lebrikizumab demonstrated variability of EOS counts across several EOS classification categories: <150 cells/ μ L; 150 to 299 cells/ μ L, and $\geq$ 300 cells/ μ L.⁶ Most patients in this *post hoc* analysis had $\geq$ 5 EOS counts during the study. Patients with baseline EOS count 150 to 299 cells/ μ L had a lower percentage of timepoints in the same classification category relative to those with baseline counts <150 cells/ μ L or $\geq$ 300 cells/ μ L. Furthermore, the percentage of patients in the same category for $\geq$ 60% of timepoints was higher than the percentage of patients in the same category for $\geq$ 90% of timepoints for all baseline categories.⁶

In the current analysis, the variability in EOS count both from baseline and at consecutive visits exhibited consistent patterns over the duration of the 52-week treatment period, and variability was observed across all baseline EOS count categories. In general, in an eosinophilic patient population (as selected by our parent study entry criteria), patients who have baseline blood EOS counts $\geq$ 400 cells/ μ L remain in that category most of the time with occasional drops into lower categories. Whereas, patients with baseline blood EOS counts <400 cells/ μ L often shift to the category of EOS $\geq$ 400 cells/ μ L at a later visit. Findings of high intra-individual variability in blood EOS count have significant implications both for clinical practice and in the research setting, particularly regarding the use of this biomarker

in making treatment decisions in patients with poorly controlled asthma and for identifying patients as having eosinophilic asthma for enrollment in clinical studies. In addition, blood EOS counts may have prognostic importance with regard to risk for future exacerbations.¹⁰ Overall, our findings support the proposal by Mathur and colleagues that repeated measurements of peripheral blood EOS count may be necessary to comprehensively identify patients eligible for diagnosis with eosinophilic asthma and treatment with anti-IL-5 mAbs.¹¹ There is a high level of variability in EOS counts even within an eosinophilic population, suggesting that a single low EOS value should not exclude a patient from anti-IL-5 therapy, and blood samples may need to be taken at multiple timepoints to fully assess the eosinophilic nature of a patient's asthma. Based on a sensitivity analysis of the current study, with 52.5% of the total variability in blood EOS counts attributable to intra-patient variability, taking two or three repeated measurements at baseline is expected to reduce the intra-patient variability by half or by two thirds. By doing so, therefore, we estimate that the total variability would be reduced by approximately 26% and 35% by two or three repeat measurements respectively.

Fifteen percent of our study cohort were receiving maintenance OCS at baseline. The proportion of patients using maintenance OCS was greatest among those in the lowest baseline EOS count category (<150 cells/ μ L; 23%). In previous studies, OCS administration has been observed to reduce blood EOS count in patients with eosinophilic asthma⁹ in a dose-dependent manner, and so this observation may be thought unsurprising.¹² However, it should be borne in mind that patients required at least one blood EOS measurement of ≥ 400 cells/ μ L during screening to be eligible to participate in the clinical study, including patients on baseline maintenance OCS.

This suggests some degree of refractoriness to the eosinopenic effects of glucocorticoids within this subpopulation. These observations warrant further study, with a view to better understanding the mechanism of this phenomenon and to further develop clinical treatment strategies for these patients.

Given the known effect of systemic corticosteroids on blood EOS counts, we performed a sensitivity analysis to assess the impact of rescue SCS on our results. Surprisingly, rescue SCS during the treatment period did not appear to have a major effect on the level of variability in EOS counts within this study population. Although patients who received rescue SCS during the treatment period had numerically slightly greater variability, both the subgroups who did or did not receive rescue SCS had similarly high levels of EOS variability over time.

The observed reduction in blood EOS count from baseline to subsequent visits in this population of patients receiving placebo may relate to improved adherence to ICS therapy in the clinical trial setting. To date, there have been few published data regarding ICS effects upon blood cell counts. Evans and colleagues demonstrated significant reductions in blood EOS during therapy with inhaled budesonide.¹³ Taken together, these findings suggest that reductions in blood EOS may be the result of local anti-inflammatory effects on airway tissue with reductions in the generation of IL-5, or might reflect systemic effects of ICS.

Our study is limited by the post hoc nature of our analysis and the relatively small number of patients in the subgroups with baseline blood EOS levels <400 cells/ μ L which is a result of the inclusion criteria to the parent phase III studies. Our analysis

is only relevant for an eosinophilic patient population (given the parent study inclusion criteria) and cannot be extrapolated to an unselected asthma population. The causes and consequences of the high degree of EOS variability observed in our placebo population, and the relationship between this variability and asthma control, are of interest. However, the current analysis did not assess the relationship between EOS fluctuations and changes in clinical outcome measures such as asthma control, nor the implications of degree of variability in EOS counts on management of severe eosinophilic asthma. We consider further investigation of the relationship between blood EOS fluctuations and clinical outcomes in dedicated studies to be warranted.

In conclusion, this *post hoc* analysis in a large cohort of patients with moderate-to-severe eosinophilic asthma who received placebo over a 52-week treatment period demonstrated the presence of substantial intra-individual variability in blood EOS count, especially in patients found to have a blood EOS count <400 cells/ μ L at the baseline visit. These findings highlight the value of conducting repeated measurements of blood EOS count in patients having or suspected of having eosinophilic asthma in order to determine if patients are appropriately eosinophilic and to prevent exclusion of eosinophilic patients from anti-IL-5 therapy based on a single blood test. This approach to the assessment of eosinophilic asthma may lead to an increased number of patients benefiting from treatment with targeted agents such as anti-IL-5 biologics. Treatment decisions informed by strengthened understanding of EOS biology could give rise to greater overall benefit and further improve patient outcomes.

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Teva employees were involved in the study design, data collection and analysis, and in the writing of this manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Figure Legends

Figure 1. Proportions of patients with shifts to a new EOS count category compared with their blood EOS count category at A) baseline and B) previous visit.

Footnotes:

A. Data are shown for change from baseline at Weeks 4, 16 and 52. The x-axis shows the post-baseline study timepoints stratified by the baseline EOS count categories. The colored bars represent the proportions of patients within each blood EOS count category at each visit (relative to their baseline category).

B. Data are shown for Weeks 4 (change from baseline), 16 (change from Week 12) and Week 52 (change from Week 48). The x-axis shows the post-baseline study timepoints stratified by the EOS count categories at the previous visit. The colored bars represent the proportions of patients within a blood EOS count category at each visit (relative to their category at each previous visit).

Figure 2. Proportions of patients in each baseline EOS count category having blood EOS counts <150 cells/ μ L over 52 weeks.

Figure 3. Absolute changes from baseline (blue) and previous visit (orange) in blood EOS count among patients receiving placebo over 52 weeks.

Footnote:

Grey line, median; white line, mean; box, 1st and 3rd quartiles.

495 **Figure 4.** Percentage changes from baseline (blue) and previous visit (orange) in
496 blood EOS count among patients receiving placebo over 52 weeks.

497 **Footnote:**

498 Grey line, median; white line, mean; box, 1st and 3rd quartiles.

499

Table I. Baseline demographic and clinical characteristics of placebo patients in the pooled analysis

Characteristic	Overall (N = 476)	Baseline blood eosinophils subgroups			
		<150 cells/ μ L (n = 31)	$\geq$ 150 to <300 cells/ μ L (n = 38)	$\geq$ 300 to <400 cells/ μ L (n = 55)	$\geq$ 400 cells/ μ L (n = 352)
Mean (SE) eosinophil count, cells/ μ L	655 (29)	81 (7)	200 (0)	300 (0)	811 (36)
Mean (SD) age, years	47.1 (14.3)	48.4 (13.9)	43.5 (16.1)	47.8 (13.3)	47.3 (14.3)
Females, n (%)	311 (65)	19 (61)	24 (63)	37 (67)	231 (66)
Mean (SD) BMI, kg/m ²	27.5 (5.7)	28.5 (6.3)	28.0 (5.6)	29.1 (6.0)	27.1 (5.5)
Mean (SD) age at asthma onset, years	27.8 (17.9)	30.4 (18.6)	21.4 (17.8)	28.2 (17.3)	28.2 (17.8)
Mean (SD) time since diagnosis, years	18.7 (13.7)	17.5 (13.4)	21.7 (15.0)	18.7 (16.6)	18.5 (13.2)
Mean (SD) FEV ₁ , L	2.0 (0.7)	1.9 (0.6)	2.2 (0.8)	2.1 (0.8)	1.9 (0.7)
Mean (SD) FEV ₁ % predicted	66.5 (19.4)	67.4 (17.9)	72.2 (18.4)	69.0 (20.8)	65.4 (19.4)
Mean (SD) ACQ-6 total score	2.5 (0.9)	2.7 (0.9)	2.5 (1.0)	2.4 (0.7)	2.5 (0.9)
Mean (SD) CAEs in previous year	2.1 (2.1)	1.9 (1.6)	1.8 (1.3)	1.8 (1.2)	2.1 (2.3)
Maintenance OCS use, n (%)	73 (15)	7 (23)	6 (16)	11 (20)	49 (14)
High-dose ICS use*, n (%)	208 (44)	12 (39)	13 (34)	27 (49)	156 (44)
LABA use, n (%)	383 (80)	25 (81)	28 (74)	42 (76)	288 (82)
High ICS/LABA use, n (%)	167 (35)	9 (29)	9 (24)	19 (35)	130 (37)

502 ACQ-6, Asthma Control Questionnaire; *BMI*, body mass index; *CAE*, clinical asthma exacerbation;
503 *ICS*, inhaled corticosteroid; *LABA*, long-acting beta₂-agonists; *FEV₁*, forced expiratory volume in 1
504 second; *OCS*, oral corticosteroid; *SD*, standard deviation; *SE*, standard error.

505 *High-dose ICS use was defined as when one of the following was true at enrollment: fluticasone
506 >500 µg/day, mometasone >440 µg/day, budesonide >800 µg/day, ciclesonide >320 µg/day,
507 beclomethasone >400 µg/day or triamcinolone >2,000 µg/day.

Table E1. Changes from baseline in patients (n [%]) in each blood eosinophil count category at each post-baseline timepoint

Baseline EOS → timepoint	Placebo (N = 476)				
	<150	≥150 to <300	≥300 to <400	≥400	Total
EOS baseline	31	38	55	352	476
Week 4	29	38	55	334	456
<150	9 (31.0)	4 (10.5)	5 (9.1)	16 (4.8)	34 (7.5)
≥150 to <300	2 (6.9)	4 (10.5)	12 (21.8)	25 (7.5)	43 (9.4)
≥300 to <400	5 (17.2)	9 (23.7)	14 (25.5)	42 (12.6)	70 (15.4)
≥400	13 (44.8)	21 (55.3)	24 (43.6)	251 (75.1)	309 (67.8)
Week 8	28	36	51	327	442
<150	8 (28.6)	5 (13.9)	3 (5.9)	31 (9.5)	47 (10.6)
≥150 to <300	3 (10.7)	10 (27.8)	11 (21.6)	17 (5.2)	41 (9.3)
≥300 to <400	3 (10.7)	6 (16.7)	10 (19.6)	38 (11.6)	57 (12.9)
≥400	14 (50.0)	15 (41.7)	27 (52.9)	241 (73.7)	297 (67.2)
Week 12	28	36	51	324	439
<150	8 (28.6)	6 (16.7)	6 (11.8)	23 (7.1)	43 (9.8)
≥150 to <300	3 (10.7)	6 (16.7)	8 (15.7)	27 (8.3)	44 (10.0)
≥300 to <400	4 (14.3)	14 (38.9)	15 (29.4)	40 (12.3)	73 (16.6)
≥400	13 (46.4)	10 (27.8)	22 (43.1)	234 (72.2)	279 (63.6)

Week 16	27	35	47	319	428
<150	10 (37.0)	9 (25.7)	5 (10.6)	16 (5.0)	40 (9.3)
≥150 to <300	3 (11.1)	10 (28.6)	7 (14.9)	36 (11.3)	56 (13.1)
≥300 to <400	3 (11.1)	3 (8.6)	16 (34.0)	40 (12.5)	62 (14.5)
≥400	11 (40.7)	13 (37.1)	19 (40.4)	227 (71.2)	270 (63.1)
Week 20	28	34	50	313	425
<150	9 (32.1)	2 (5.9)	8 (16.0)	22 (7.0)	41 (9.6)
≥150 to <300	3 (10.7)	6 (17.6)	8 (16.0)	20 (6.4)	37 (8.7)
≥300 to <400	2 (7.1)	8 (23.5)	12 (24.0)	29 (9.3)	51 (12.0)
≥400	14 (50.0)	18 (52.9)	22 (44.0)	242 (77.3)	296 (69.6)
Week 24	26	35	49	303	413
<150	12 (46.2)	4 (11.4)	9 (18.4)	21 (6.9)	46 (11.1)
≥150 to <300	4 (15.4)	7 (20.0)	8 (16.3)	32 (10.6)	51 (12.3)
≥300 to <400	3 (11.5)	12 (34.3)	14 (28.6)	33 (10.9)	62 (15.0)
≥400	7 (26.9)	12 (34.3)	18 (36.7)	217 (71.6)	254 (61.5)
Week 28	26	35	47	306	414
<150	6 (23.1)	4 (11.4)	8 (17.0)	19 (6.2)	37 (8.9)
≥150 to <300	8 (30.8)	6 (17.1)	8 (17.0)	26 (8.5)	48 (11.6)
≥300 to <400	4 (15.4)	9 (25.7)	7 (14.9)	37 (12.1)	57 (13.8)

≥400	8 (30.8)	16 (45.7)	24 (51.1)	224 (73.2)	272 (65.7)
Week 32	27	33	51	303	414
<150	8 (29.6)	4 (12.1)	6 (11.8)	26 (8.6)	44 (10.6)
≥150 to <300	3 (11.1)	11 (33.3)	11 (21.6)	21 (6.9)	46 (11.1)
≥300 to <400	6 (22.2)	7 (21.2)	14 (27.5)	35 (11.6)	62 (15.0)
≥400	10 (37.0)	11 (33.3)	20 (39.2)	221 (72.9)	262 (63.3)
Week 36	26	32	49	300	407
<150	8 (30.8)	4 (12.5)	10 (20.4)	28 (9.3)	50 (12.3)
≥150 to <300	5 (19.2)	6 (18.8)	4 (8.2)	24 (8.0)	39 (9.6)
≥300 to <400	1 (3.8)	8 (25.0)	11 (22.4)	27 (9.0)	47 (11.5)
≥400	12 (46.2)	14 (43.8)	24 (49.0)	221 (73.7)	271 (66.6)
Week 40	24	34	48	304	410
<150	6 (25.0)	2 (5.9)	9 (18.8)	20 (6.6)	37 (9.0)
≥150 to <300	2 (8.3)	12 (35.3)	11 (22.9)	25 (8.2)	50 (12.2)
≥300 to <400	3 (12.5)	7 (20.6)	10 (20.8)	37 (12.2)	57 (13.9)
≥400	13 (54.2)	13 (38.2)	18 (37.5)	222 (73.0)	266 (64.9)
Week 44	26	33	50	303	412
<150	7 (26.9)	3 (9.1)	6 (12.0)	24 (7.9)	40 (9.7)
≥150 to <300	3 (11.5)	2 (6.1)	10 (20.0)	20 (6.6)	35 (8.5)

≥300 to <400	6 (23.1)	10 (30.3)	11 (22.0)	42 (13.9)	69 (16.7)
≥400	10 (38.5)	18 (54.5)	23 (46.0)	217 (71.6)	268 (65.0)
Week 48	24	34	49	297	404
<150	8 (33.3)	3 (8.8)	8 (16.3)	29 (9.8)	48 (11.9)
≥150 to <300	4 (16.7)	9 (26.5)	8 (16.3)	23 (7.7)	44 (10.9)
≥300 to <400	1 (4.2)	3 (8.8)	9 (18.4)	32 (10.8)	45 (11.1)
≥400	11 (45.8)	19 (55.9)	24 (49.0)	213 (71.7)	267 (66.1)
Week 52	26	34	47	298	405
<150	9 (34.6)	3 (8.8)	8 (17.0)	22 (7.4)	42 (10.4)
≥150 to <300	4 (15.4)	4 (11.8)	6 (12.8)	23 (7.7)	37 (9.1)
≥300 to <400	6 (23.1)	8 (23.5)	11 (23.4)	48 (16.1)	73 (18.0)
≥400	7 (26.9)	19 (55.9)	22 (46.8)	205 (68.8)	253 (62.5)

Table E2. Changes from previous visit in patients (n [%]) in each blood eosinophil count category at each post-baseline timepoint

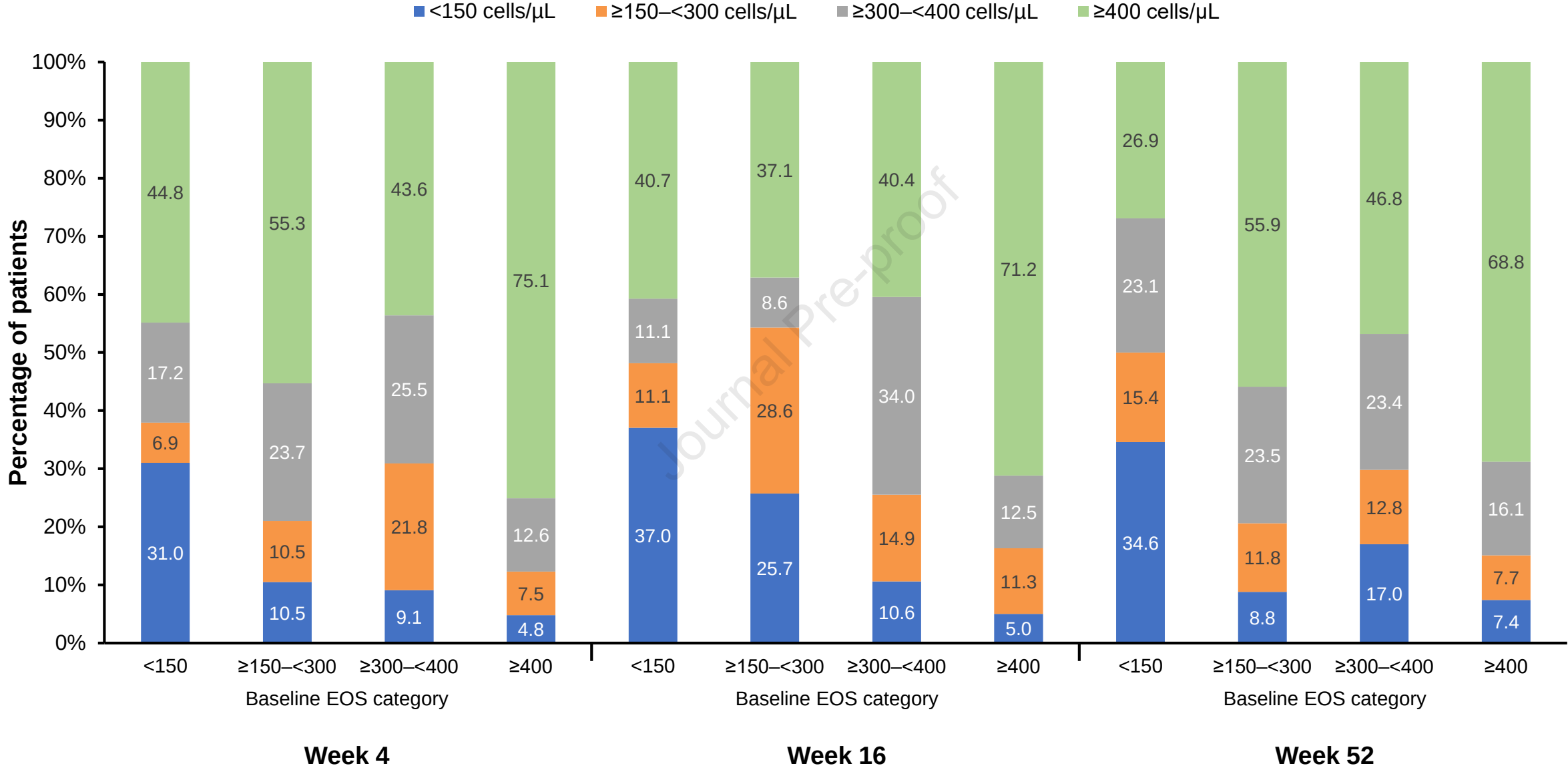
Previous visit EOS → timepoint	Placebo N = 476				
	<150	≥150 to <300	≥300 to <400	≥400	Total
Baseline	31	38	55	352	476
Week 4	29	38	55	334	456
<150	9 (31.0)	4 (10.5)	5 (9.1)	16 (4.8)	34 (7.5)
≥150 to <300	2 (6.9)	4 (10.5)	12 (21.8)	25 (7.5)	43 (9.4)
≥300 to <400	5 (17.2)	9 (23.7)	14 (25.5)	42 (12.6)	70 (15.4)
≥400	13 (44.8)	21 (55.3)	24 (43.6)	251 (75.1)	309 (67.8)
Week 8	31	41	68	292	432
<150	10 (32.3)	6 (14.6)	6 (8.8)	21 (7.2)	43 (10.0)
≥150 to <300	7 (22.6)	9 (22.0)	12 (17.6)	13 (4.5)	41 (9.5)
≥300 to <400	5 (16.1)	4 (9.8)	17 (25.0)	30 (10.3)	56 (13.0)
≥400	9 (29.0)	22 (53.7)	33 (48.5)	228 (78.1)	292 (67.6)
Week 12	46	38	54	286	424
<150	11 (23.9)	3 (7.9)	8 (14.8)	16 (5.6)	38 (9.0)
≥150 to <300	7 (15.2)	10 (26.3)	7 (13.0)	17 (5.9)	41 (9.7)
≥300 to <400	10 (21.7)	11 (28.9)	15 (27.8)	36 (12.6)	72 (17.0)

≥400	18 (39.1)	14 (36.8)	24 (44.4)	217 (75.9)	273 (64.4)
Week 16	40	42	69	266	417
<150	14 (35.0)	5 (11.9)	9 (13.0)	12 (4.5)	40 (9.6)
≥150 to <300	11 (27.5)	14 (33.3)	11 (15.9)	19 (7.1)	55 (13.2)
≥300 to <400	3 (7.5)	7 (16.7)	15 (21.7)	32 (12.0)	57 (13.7)
≥400	12 (30.0)	16 (38.1)	34 (49.3)	203 (76.3)	265 (63.5)
Week 20	39	49	60	264	412
<150	12 (30.8)	5 (10.2)	11 (18.3)	12 (4.5)	40 (9.7)
≥150 to <300	6 (15.4)	8 (16.3)	8 (13.3)	14 (5.3)	36 (8.7)
≥300 to <400	5 (12.8)	13 (26.5)	8 (13.3)	25 (9.5)	51 (12.4)
≥400	16 (41.0)	23 (46.9)	33 (55.0)	213 (80.7)	285 (69.2)
Week 24	37	36	50	281	404
<150	15 (40.5)	6 (16.7)	3 (6.0)	22 (7.8)	46 (11.4)
≥150 to <300	10 (27.0)	7 (19.4)	14 (28.0)	19 (6.8)	50 (12.4)
≥300 to <400	6 (16.2)	13 (36.1)	13 (26.0)	30 (10.7)	62 (15.3)
≥400	6 (16.2)	10 (27.8)	20 (40.0)	210 (74.7)	246 (60.9)
Week 28	45	49	60	243	397
<150	14 (31.1)	5 (10.2)	3 (5.0)	14 (5.8)	36 (9.1)
≥150 to <300	8 (17.8)	13 (26.5)	15 (25.0)	10 (4.1)	46 (11.6)

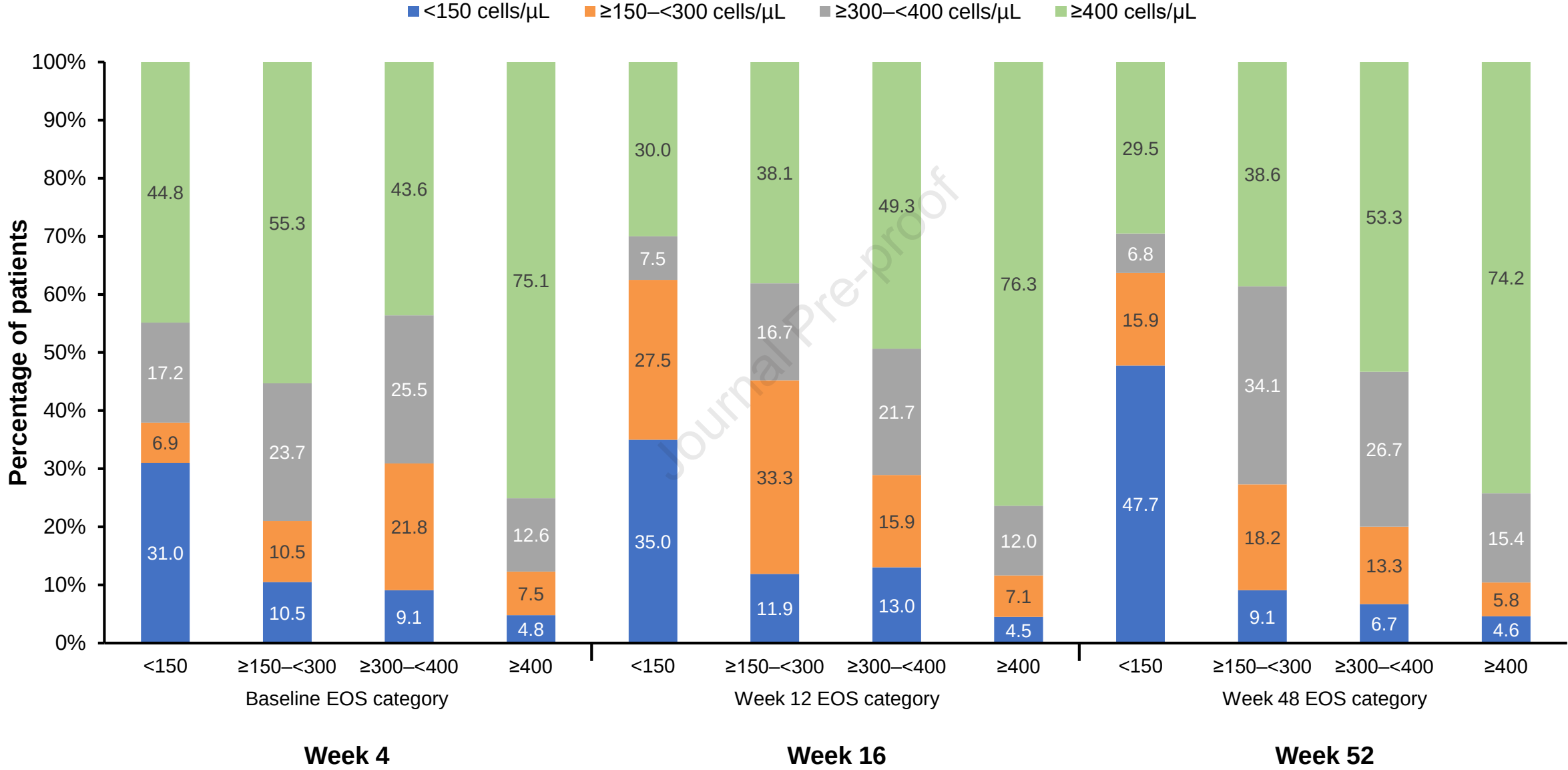
≥300 to <400	8 (17.8)	17 (34.7)	13 (21.7)	18 (7.4)	56 (14.1)
≥400	15 (33.3)	14 (28.6)	29 (48.3)	201 (82.7)	259 (65.2)
Week 32	37	46	54	262	399
<150	10 (27.0)	12 (26.1)	6 (11.1)	13 (5.0)	41 (10.3)
≥150 to <300	9 (24.3)	11 (23.9)	14 (25.9)	9 (3.4)	43 (10.8)
≥300 to <400	8 (21.6)	11 (23.9)	16 (29.6)	23 (8.8)	58 (14.5)
≥400	10 (27.0)	12 (26.1)	18 (33.3)	217 (82.8)	257 (64.4)
Week 36	44	42	59	251	396
<150	16 (36.4)	10 (23.8)	4 (6.8)	20 (8.0)	50 (12.6)
≥150 to <300	8 (18.2)	8 (19.0)	14 (23.7)	9 (3.6)	39 (9.8)
≥300 to <400	6 (13.6)	9 (21.4)	11 (18.6)	18 (7.2)	44 (11.1)
≥400	14 (31.8)	15 (35.7)	30 (50.8)	204 (81.3)	263 (66.4)
Week 40	47	39	46	262	394
<150	16 (34.0)	5 (12.8)	1 (2.2)	13 (5.0)	35 (8.9)
≥150 to <300	10 (21.3)	8 (20.5)	9 (19.6)	20 (7.6)	47 (11.9)
≥300 to <400	7 (14.9)	12 (30.8)	12 (26.1)	24 (9.2)	55 (14.0)
≥400	14 (29.8)	14 (35.9)	24 (52.2)	205 (78.2)	257 (65.2)
Week 44	35	48	56	260	399
<150	12 (34.3)	7 (14.6)	6 (10.7)	14 (5.4)	39 (9.8)

≥150 to <300	6 (17.1)	8 (16.7)	7 (12.5)	11 (4.2)	32 (8.0)
≥300 to <400	6 (17.1)	12 (25.0)	21 (37.5)	29 (11.2)	68 (17.0)
≥400	11 (31.4)	21 (43.8)	22 (39.3)	206 (79.2)	260 (65.2)
Week 48	38	35	65	261	399
<150	15 (39.5)	7 (20.0)	10 (15.4)	16 (6.1)	48 (12.0)
≥150 to <300	6 (15.8)	8 (22.9)	11 (16.9)	17 (6.5)	42 (10.5)
≥300 to <400	4 (10.5)	7 (20.0)	12 (18.5)	21 (8.0)	44 (11.0)
≥400	13 (34.2)	13 (37.1)	32 (49.2)	207 (79.3)	265 (66.4)
Week 52	44	44	45	260	393
<150	21 (47.7)	4 (9.1)	3 (6.7)	12 (4.6)	40 (10.2)
≥150 to <300	7 (15.9)	8 (18.2)	6 (13.3)	15 (5.8)	36 (9.2)
≥300 to <400	3 (6.8)	15 (34.1)	12 (26.7)	40 (15.4)	70 (17.8)
≥400	13 (29.5)	17 (38.6)	24 (53.3)	193 (74.2)	247 (62.8)

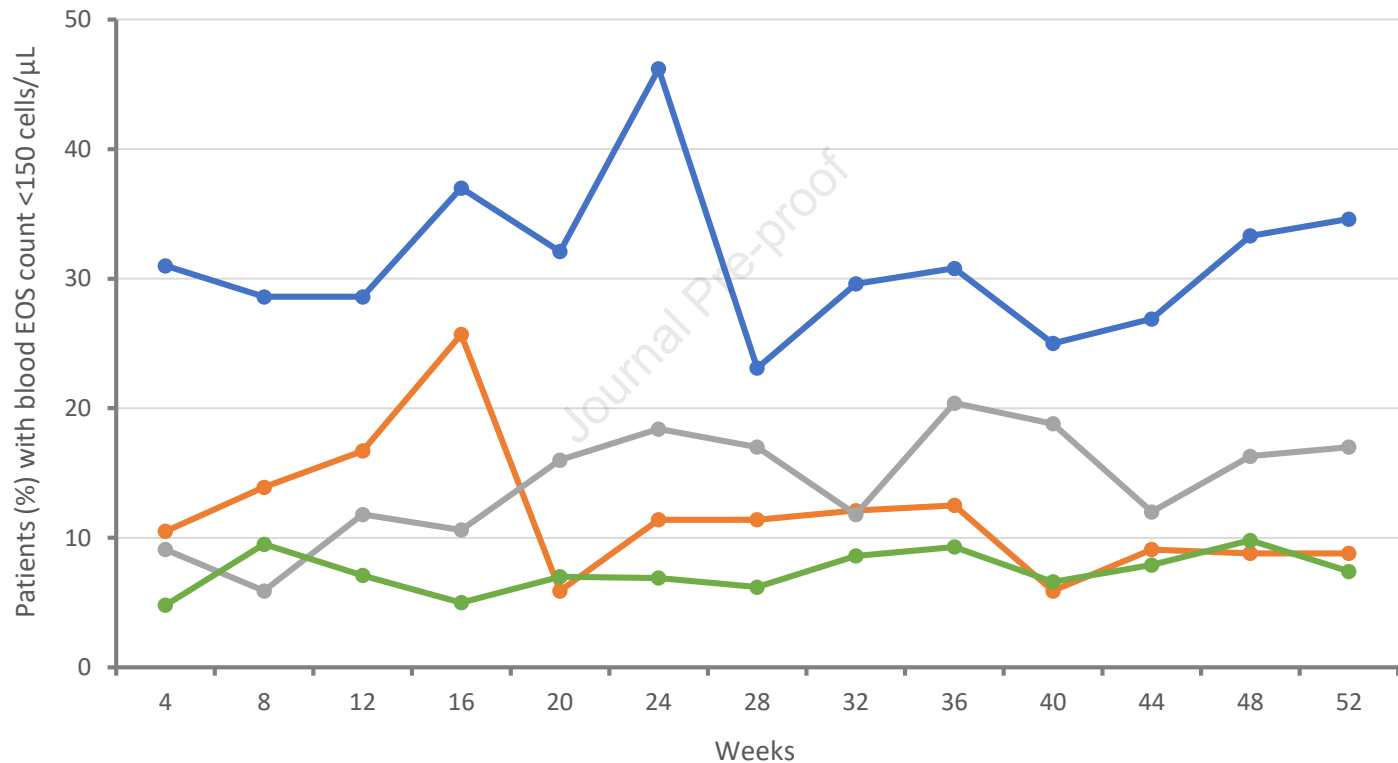
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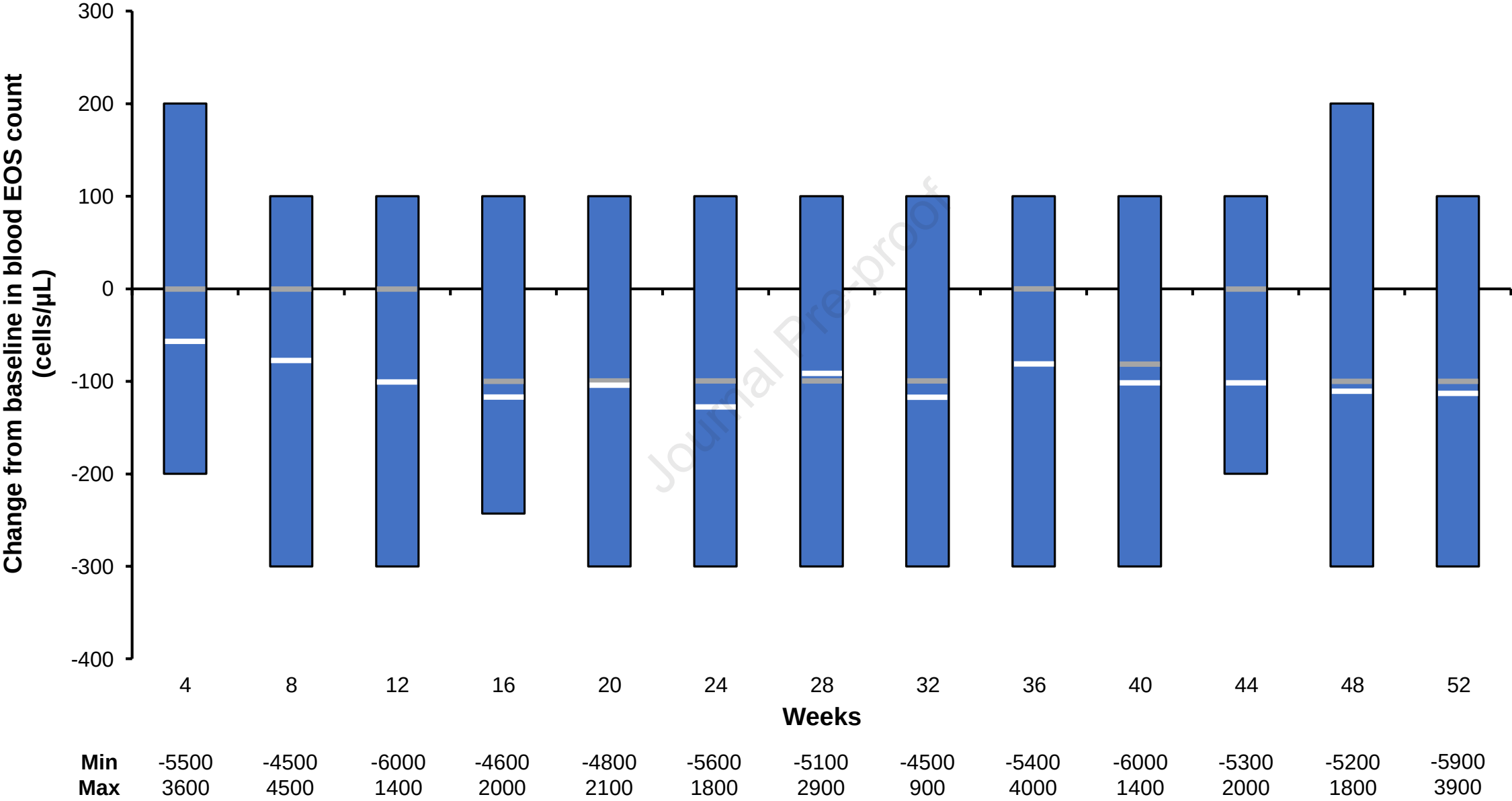
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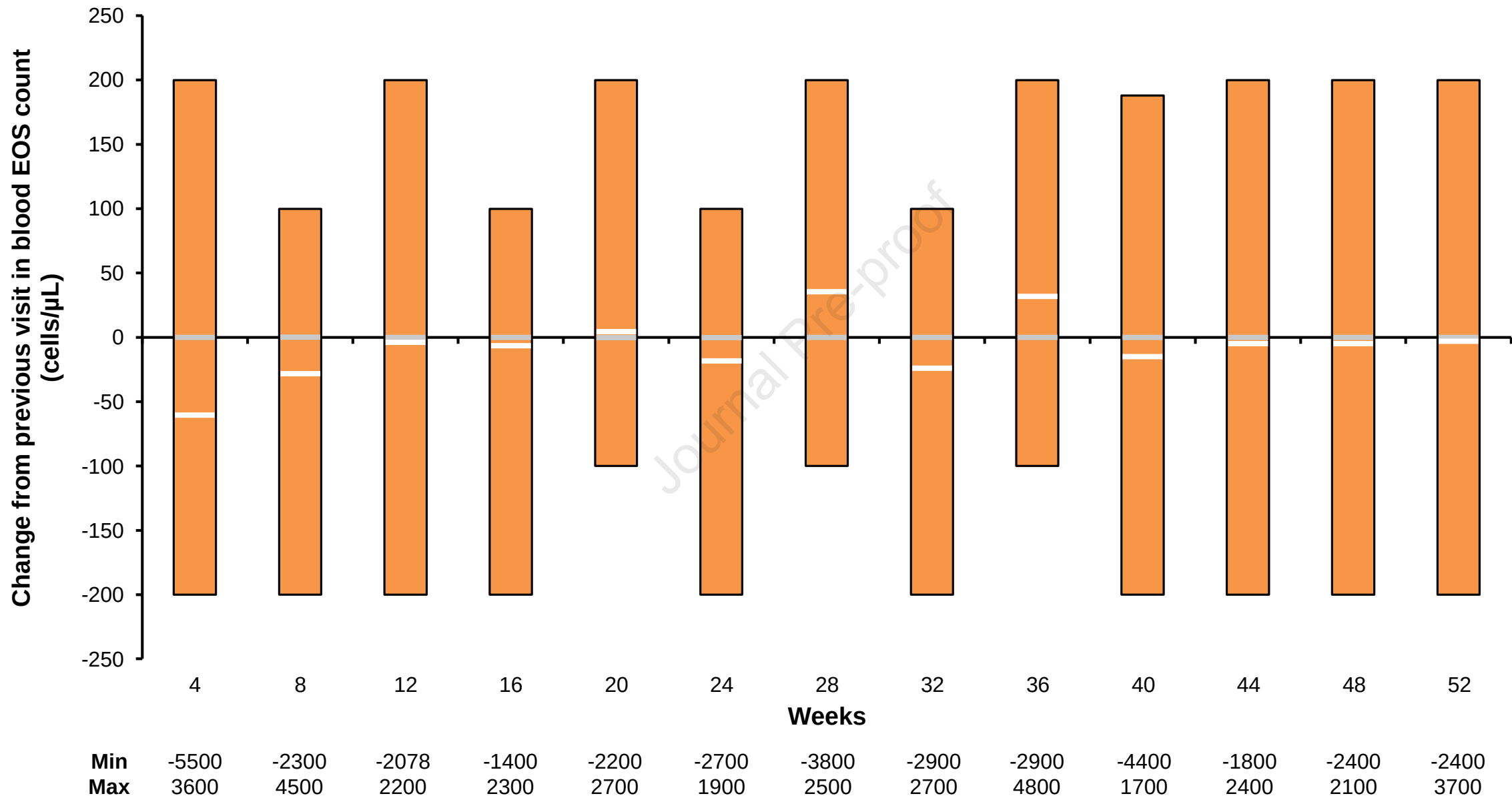
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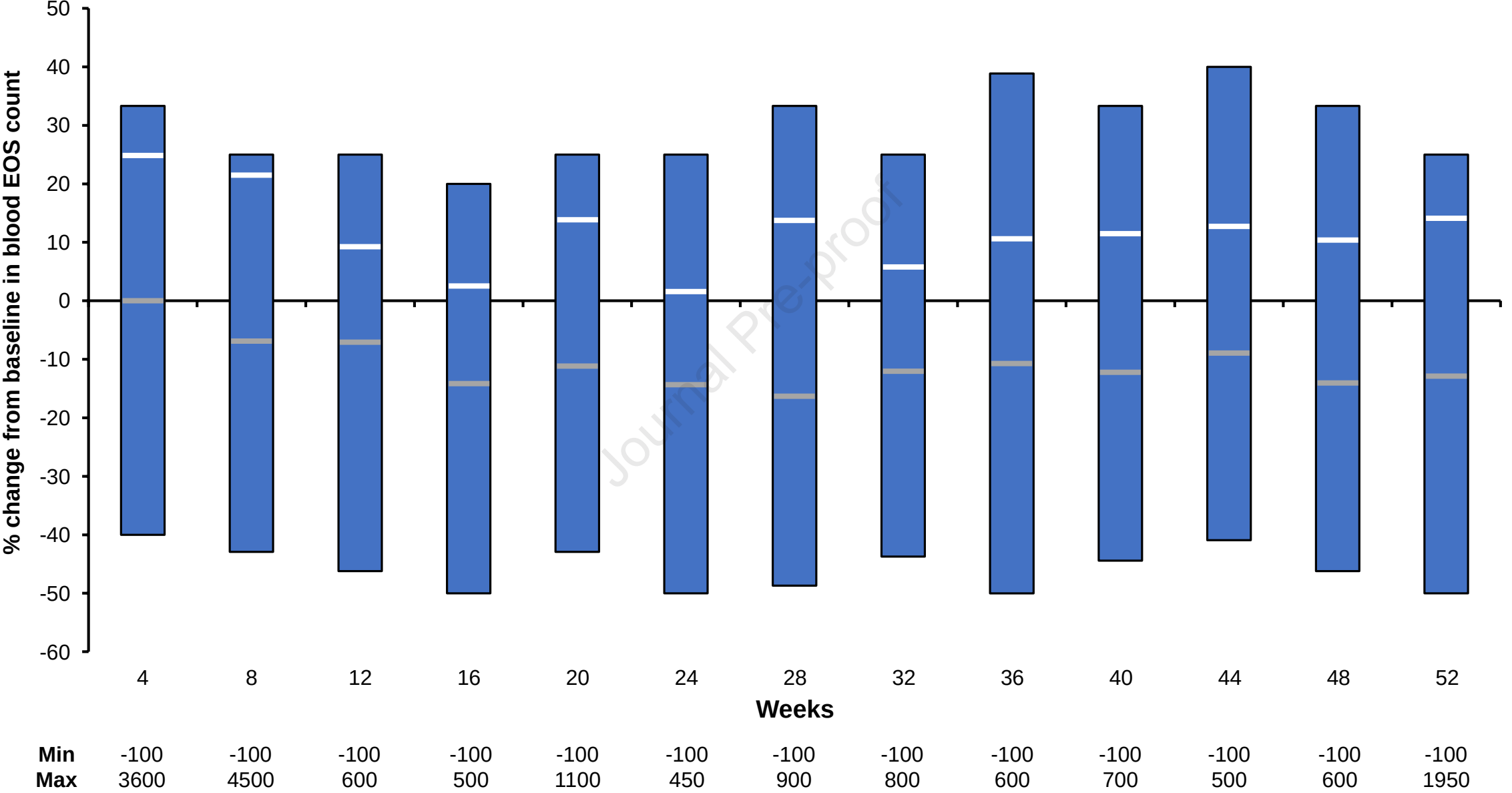
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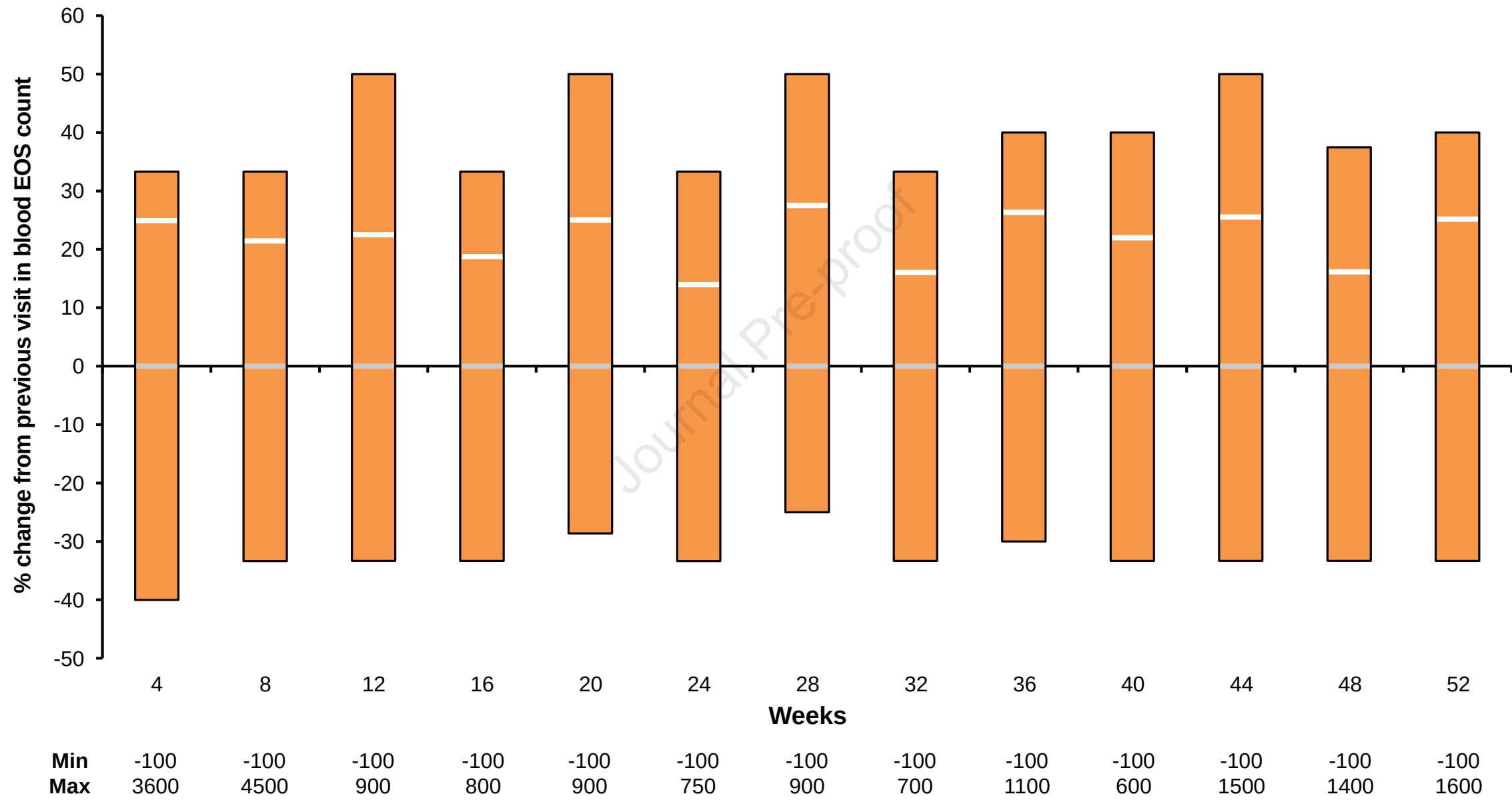
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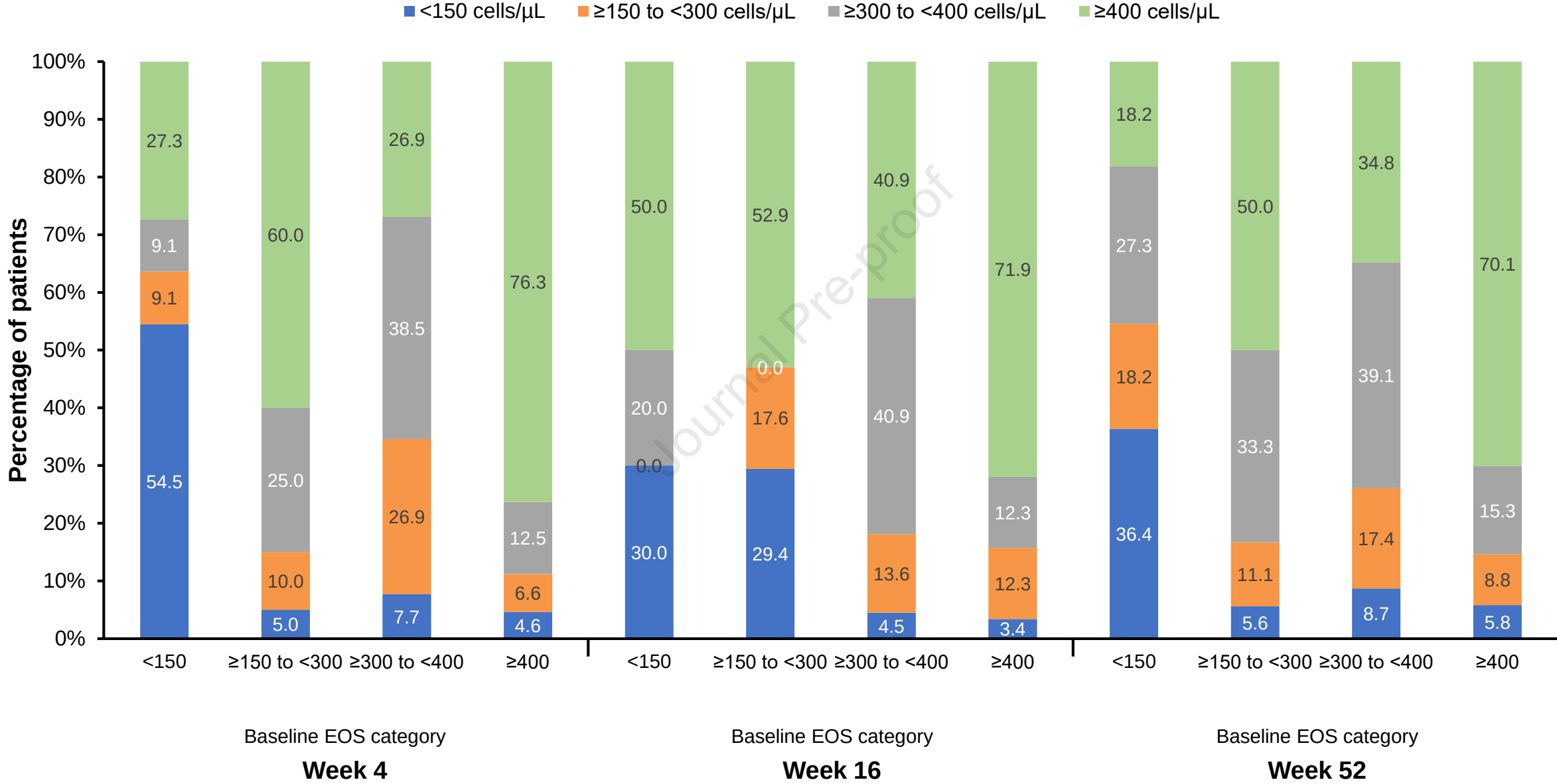


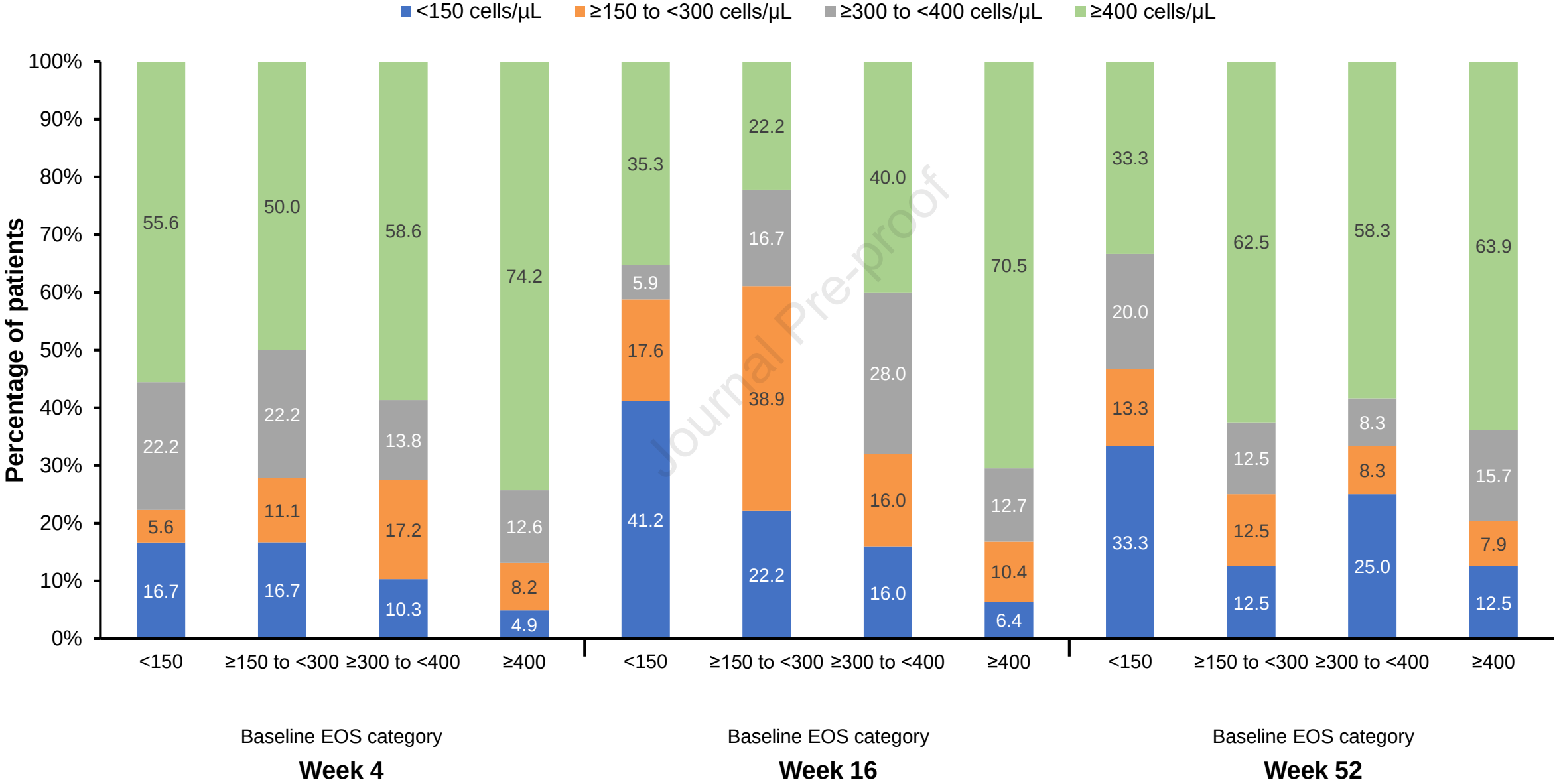
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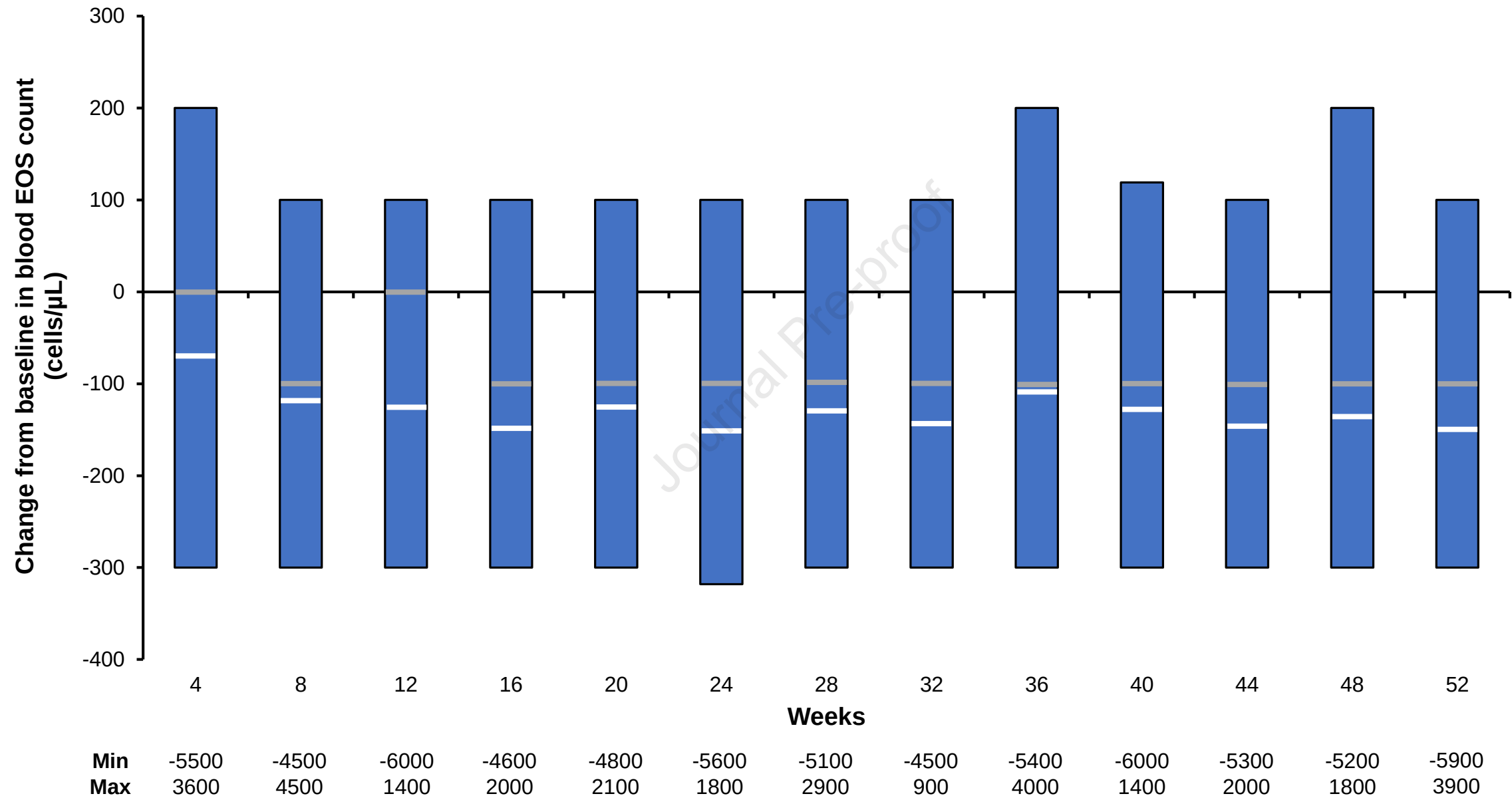
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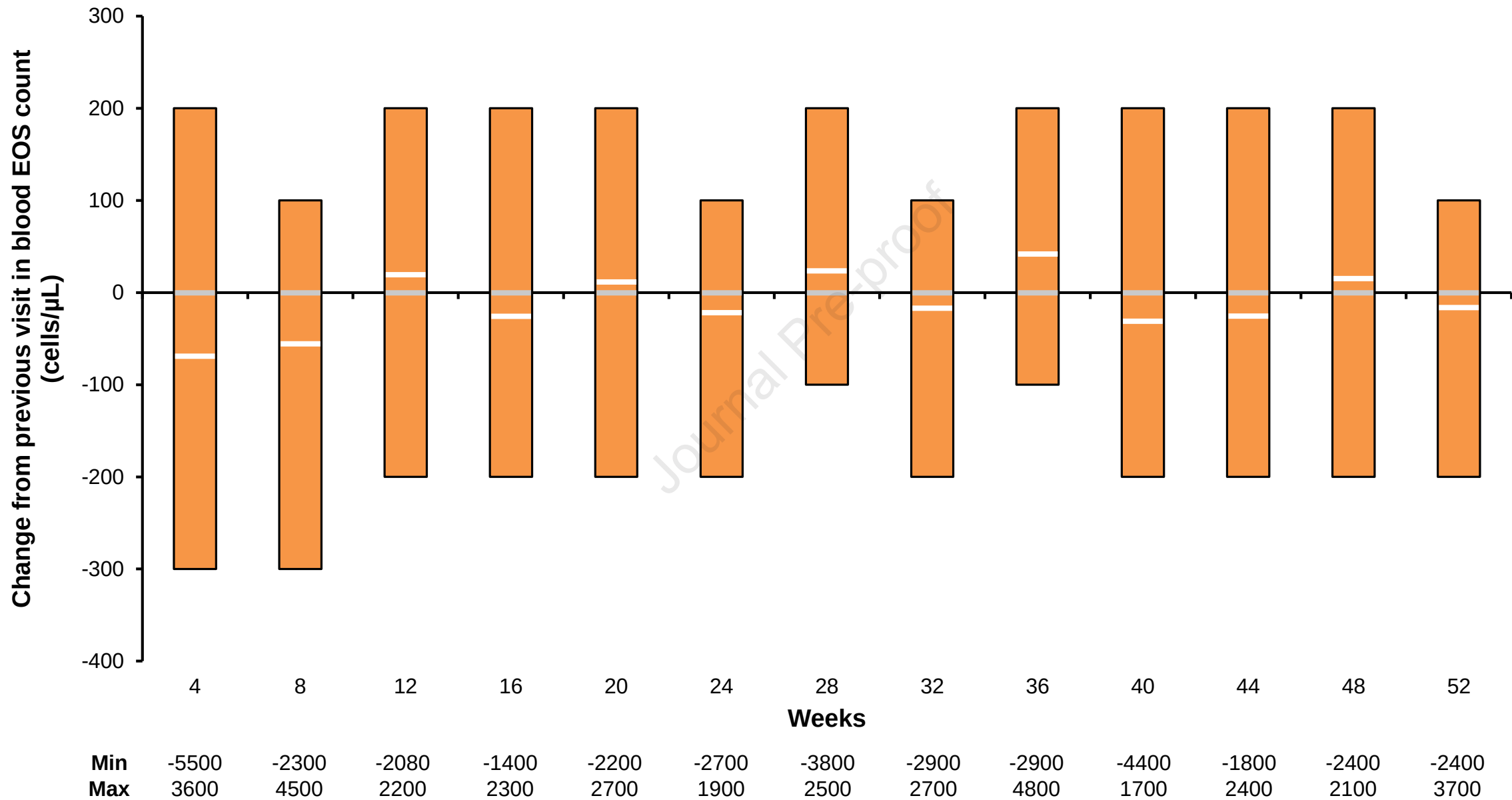




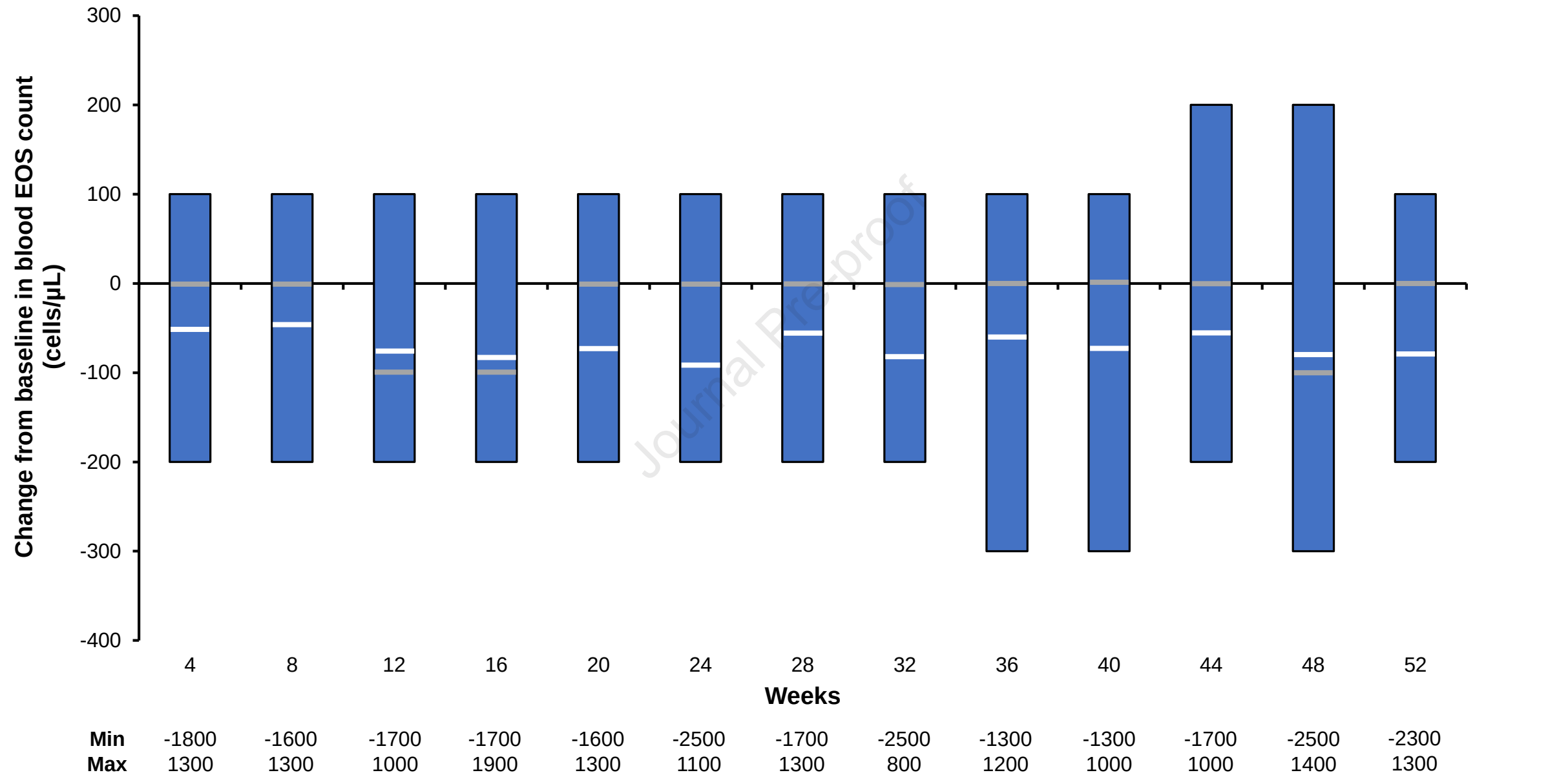
A – Patients with SCS



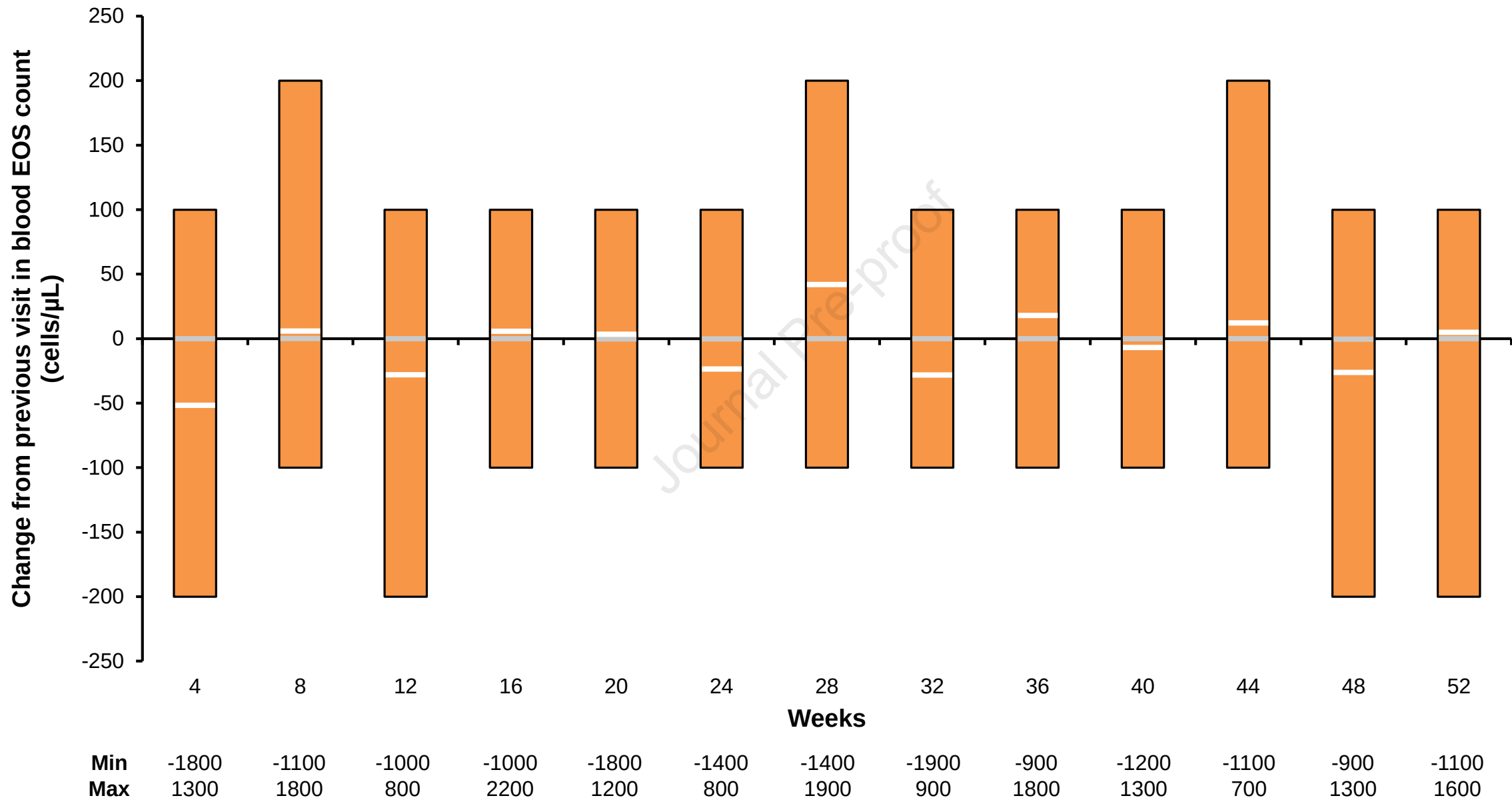
B – Patients with SCS



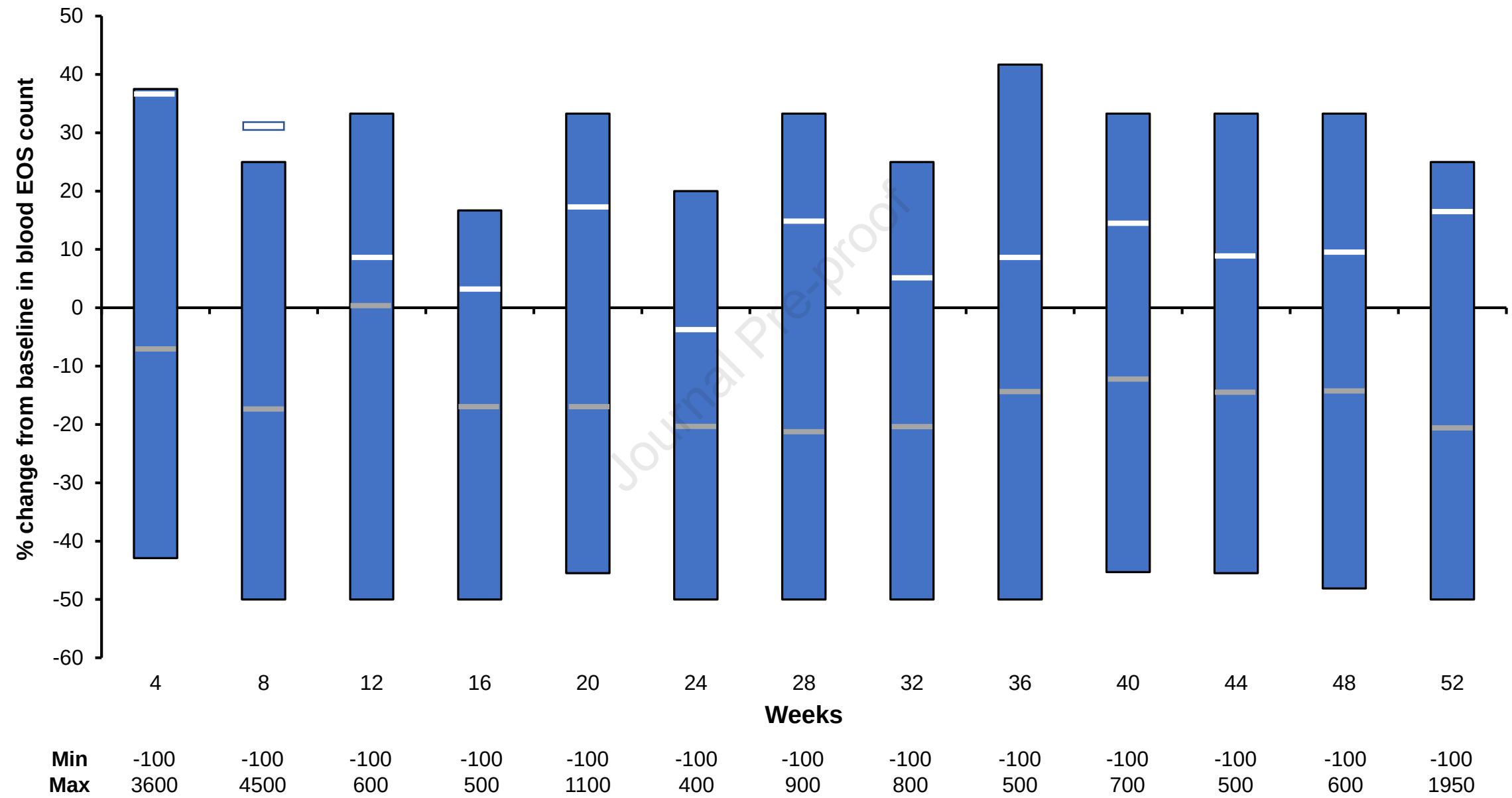
C – Patients without SCS



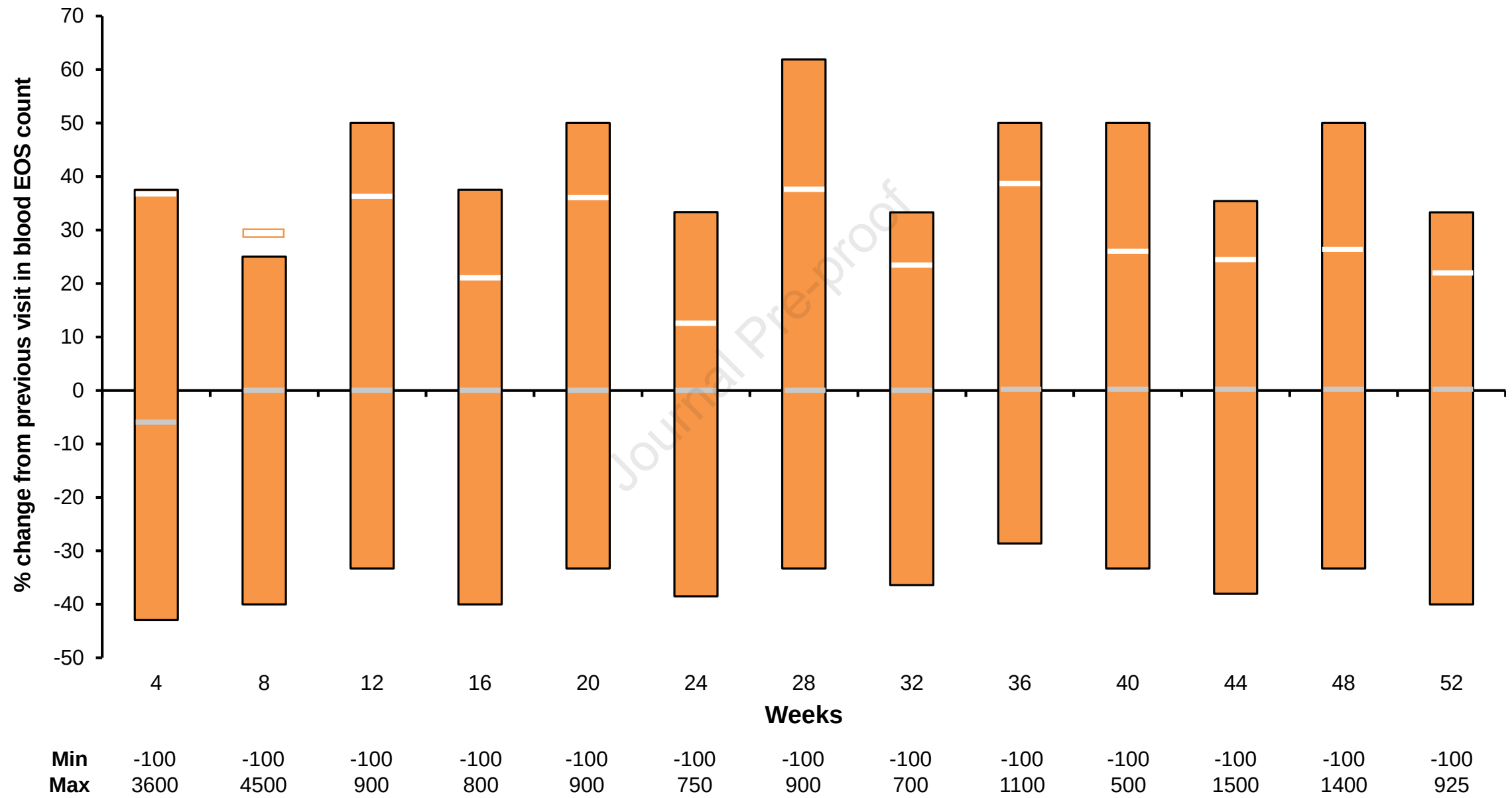
D – Patients without SCS



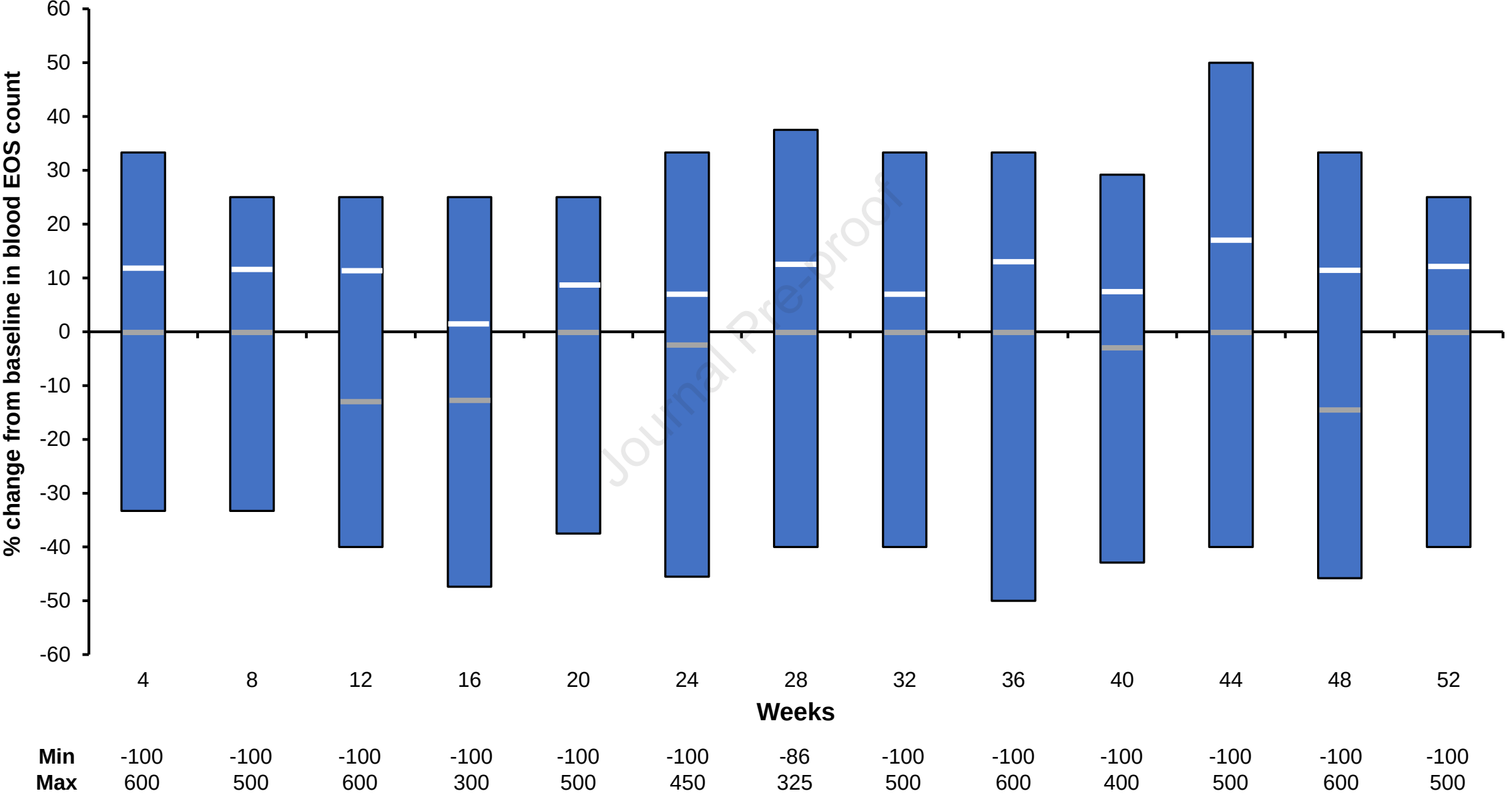
A – Patients with SCS



B – Patients with SCS



C – Patients without SCS



D – Patients without SCS

