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Running Head: Remission and Complete Response in Chronic Gout

Evaluation of Proposed Criteria for Remission and Evidence Based Development of Criteria for Complete Response in Patients with Chronic Refractory Gout

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ABSTRACT

Objective: To assess criteria for gout remission and to use the results to inform criteria for a complete response (CR).

Methods: Post-hoc analysis of two clinical trials were undertaken to determine the frequency with which pegloticase-treated subjects with chronic refractory gout met remission criteria. Mixed modelling was then employed to identify the components that best correlated with time to maximum benefit.

Results: Of 56 subjects treated with biweekly pegloticase for whom adequate data were collected, 48.2% met the remission criteria. When subjects with persistent urate lowering were examined separately, 27 of 32 (84.4%) met the criteria for remission. In contrast, even when the requirement for serum urate lowering was waived, only 2 of 24 (8.3%) of those without persistent urate lowering and 0 of 43 subjects receiving placebo met criteria. Mixed modelling indicated that in addition to urate levels, assessment of tophi, swollen joints, tender joints, and patient global assessment best correlated with time to maximum benefit. Using these criteria of CR, 23 of the responders (71.9%) met the criteria. All patients who achieved a CR maintained it for a mean duration of 507.4 days. Finally, 64% of persistent responders to monthly pegloticase also met criteria for CR.

Conclusion: These results have validated the proposed remission criteria for gout and helped define criteria for CR in individuals with chronic gout treated with pegloticase. This composite CR Index can serve as an evidence-based target to inform the design and endpoints of future clinical trials.

Significance and Innovations

- A post-hoc analysis of data from published RCTs of pegloticase in chronic refractory gout clearly documented the ability of the proposed remission criteria in gout to

distinguish subjects who had persistent urate lowering from those who had only transient lowering or received placebo.

- Using these results and mixed modeling, novel evidence-based criteria for a complete response were generated and tested using the data from the pegloticase trials.
- 71.9% of persistent responders to pegloticase met the criteria of a complete response in a mean time of 346 days
- These composite outcome measures should be useful as endpoints in clinical trials and treat to target strategies.

Key Words: gout, serum urate, remission, outcome

Treating to target is an approach to disease management that considers well-defined physiologic targets for controlling disease activity and the means to achieve them.[1] This approach has become the standard of care in many chronic diseases, including hypertension, coronary artery disease, diabetes, and rheumatoid arthritis[2,3], and a treat-to-target approach has been suggested for gout.[1,4-6] However, the treatment goals for patients with this disease have not been fully defined.[7-9]

Treatment goals for gout have typically focused on the biochemical response to treatment (i.e., lowering serum urate to <6 mg/dL) and to even lower levels in selected patients, such as those with extensive monosodium urate (MSU) crystal deposition.[7-9] However, reaching these levels does not guarantee achievement of clinical goals. Gout

flares may still occur despite urate levels <6.8 mg/dL, the saturation level for urate, possibly because of persistent tophi and an increased body urate pool.[10]

It is likely that in subjects with chronic or advanced gout, the focus on serum urate to define success of gout treatment is too narrow and that clinical goals may vary based on factors including the burden of MSU crystal deposition, the nature of the clinical manifestation, and expectations of patients.[11,12] In subjects with advanced gout, resolution of tophi is a major goal of treatment, but it is difficult to achieve with current oral urate lowering therapy. Even though the development of tophi in subjects with gout is related to the serum urate level and the duration of hyperuricemia,[13] the relationship between urate and tophus development is not precise as only 50% of subjects develop obvious tophi within 10 years of an initial gout flare, whereas 28% remain free of tophi even 20 years after an initial gout flare.[14] Moreover, even though the velocity of reduction of tophus burden is correlated with serum urate levels, the correlations reported are modest (r= 0.4 and 0.6)[15,16] indicating that other variables influence this process.

Composite indices have been developed to assess the activity of gout and one of these, the Gout Activity Score (GAS) has recently been demonstrated to be sensitive to change.[17-19] However, the GAS measures the level of disease activity in a number of domains and does not provide a target for remission of gout activity. A recent Delphi exercise focused on defining criteria for remission in gout and reached consensus on a multidimensional definition that included serum urate <6 mg/dL, no flares, resolution of all tophi, limited pain, and low patient global assessment of disease activity, each with a score <2 on a 10 cm visual analog scale.[20] Although these proposed remission domains have some overlap with those of GAS, they are not identical, including pain as an outcome. Moreover, the remission criteria encompass specific goals to be achieved to consider a subject to have achieved remission. Although the criteria for remission were proposed, they have not been tested in longitudinal clinical trials. Moreover, their utility in chronic or advanced gout have not been examined.

This study therefore, evaluated the utility of these proposed criteria using clinical results from patients with chronic refractory gout who received pegloticase (8 mg every 2 weeks), a mammalian recombinant uricase conjugated to polyethylene glycol that is approved for treatment of adult patients with chronic gout refractory to oral urate lowering therapy. Specifically, all clinical data from subjects collected at each clinical visit were evaluated by an independent investigator to determine whether the subject met remission criteria at that visit.[20]

PATIENTS AND METHODS

Design of Pegloticase Clinical Trials

Results from two identical randomized controlled trials (RCTs) of pegloticase and their open-label extension (OLE) (NCT00325195, NCT01356498) were analyzed. The methods for these studies have been described in detail, and they will be summarized only briefly here.[21,22]

Patients were ≥18 years of age with chronic refractory gout, defined as baseline sUA ≥8.0 mg/dL, and ≥1 of the following: 1) ≥3 self-reported gout flares during the previous 18 months; 2) ≥1 tophi; and 3) gouty arthropathy, defined clinically or radiographically as joint damage caused by gout; and contraindication to treatment with allopurinol or history of failure to normalize sUA despite ≥3 months of treatment with the maximum medically appropriate allopurinol dose as determined by the treating physician. Patients were randomized to 6 months of treatment with intravenous infusions of either pegloticase 8 mg at each infusion, pegloticase 8 mg alternating with placebo, or placebo.[21] Flare prevention medication (hydrocortisone and anti-histamines) was given to all subjects. After the RCT, subjects were given the option of entering an OLE to assess the persistence of the response.

A responder to treatment (primary endpoint for the RCTs) was defined as a patient with serum urate <6.0 mg/dL for ≥80% of the time during months 3 and 6. Nonresponders were all other subjects, including those who left the study early. Secondary endpoints

included tophus resolution; reductions in the proportion of patients with gout flares and in the number of flares per patient during months 1-3 and 4-6 of the trial; reductions in tender and swollen joint counts; and, patient-reported changes in pain, physical function, and quality of life, measured respectively, by the Health Assessment Questionnaire (HAQ) pain scale, HAQ–Disability Index (HAQ-DI), and 36-Item Short Form Health Survey (SF-36).[21] This study was completed before the remission criteria were proposed, and remission was not an outcome measure.

Tophus assessment was carried out using Computer Assisted Photographic Evaluation in Rheumatology (CAPER) methodology.[23] Photographs of the hands and feet were taken for each patient at baseline. Photographs of up to two additional regions were taken at the discretion of the investigator based on other tophi identified at baseline. Digital media cards containing the photographs were sent to RadPharm (Princeton, NJ, USA) where central readers, who were blinded to treatment assignment, evaluated the photographs prospectively and identified sites of tophi present at the start of treatment as well as response to therapy. Patients completing either of two replicate RCTs were eligible to enter an open-label extension (OLE) for up to 3 years in which they received pegloticase 8 mg every 2 weeks. Safety was evaluated as the primary outcome, but the above described efficacy variables were also assessed.[22]

Relating Clinical Responses to Published Criteria for Gout Remission

Of the 85 subjects who entered the RCTs and received pegloticase 8 mg biweekly, a total of 56 proceeded into the OLE and sufficient data were collected to assess whether they met criteria of remission. Of these subjects, 36 were responders to treatment in the RCTs (persistent serum urate <6mg/dL), 34 of these subjects entered the OLE[20], and 32 had adequate data collected to assess. Of those without persistent urate lowering in the RCT (nonresponders), 24 proceeded into the OLE and had sufficient data collected to be analyzed. Initially, individual patient data from each clinic visit was reviewed by an independent evaluator to establish the frequency with which subjects met the proposed remission criteria. To be classified as meeting remission criteria, a subject was required to have a serum urate <6mg/dL, no flares during the time since the last visit, no detectable tophi, and pain and patient global assessment <2 on a 10 cm visual analog scale. Only subjects who met all 5 criteria were considered to meet criteria of remission. Subsequently, this group of subjects was employed to determine new criteria for a "complete response" (CR) by using mixed modelling. A repeated measures, mixed effects model controlling for repeated observations was used to relate the time when a response was noted in patient global assessment (PGA) scores, SF-36 bodily pain scores, VAS pain levels, number of tender joints (TJC), number of swollen joints (SJC), the number of flare episodes, and the degree of tophus resolution. Variables were then excluded by using backward elimination of the least statistically significant term. The final model included all terms that were statistically significant. The results from the analysis of patients who responded to administration of pegloticase every 2 weeks was validated with a second analysis of results for patients who responded to administration of pegloticase every 4-weeks in the RCTs.

Additional analyses carried out using results from this patient cohort included: 1) time to achieve remission according to the criteria set forth in the Delphi exercise[20]; 2) correlations among components of remission and CR for patients meeting the criteria for remission; 3) the relationship between flares, serum urate levels, and clinical characteristics for patients meeting the criteria for remission; 4) time to CR for all

responders in the RCTs for pegloticase; and, 5) the relationship between time to achieve CR and duration of that response.

The relationships between flares and other clinical variables, tender and swollen joint counts, VAS pain, SF-36 pain, PGA, percent reduction from baseline in tophus area, and sUA, were also evaluated for all 56 patients (responders and non-responders) who were treated with pegloticase every 2 weeks in the RCTs and who continued into the OLE. Each subject was evaluated every 2 weeks and if a flare was reported the values for all measures were evaluated at the subsequent visit to determine the association with the flare. If no flare was reported for the 2 weeks before the evaluation, all measures were considered to be unrelated to flares. Values for each measure that were associated or not associated with flares were compared with Wilcoxon signed-ranks tests.

RESULTS

Achievement of Remission

Of 56 evaluable subjects treated with biweekly pegloticase, 27 (48.2%) met criteria for remission (**Figure 1A**). Since this group of subjects included both those who had persistent urate lowering in response to pegloticase (n=32) and those with only transient urate lowering (n= 24), it was of interest to determine whether the attainment of remission was associated with persistent urate lowering. Of the 32 pegloticase responders in the RCTs who entered the OLE, 27 (84.4%) met the criteria for remission (**Figure 1B**). When the requirement of serum urate <6 mg/dL was waived, only 2 of 24 (8.3%) of nonresponders and 0 of 43 (0.0%) of subjects receiving placebo met clinical criteria for remission. The times to achieve remission for all pegloticase responders in the RCTs and for those who met the criteria for remission are shown in **Figure 1B**. The length of time required for 50% of patients to achieve remission was 252 days (8.4 months) for all responders and 181 days (6.0 months) for responders who achieved remission.

Relationships between Flares, Serum Urate Levels and Patient Clinical Characteristics

In order to determine whether the various domains of the "remission" model contributed information, we attempted to develop correlations between the various components. First, we assessed relationships between gout flares and other variables. As can be seen in **Figure 2**, all clinical variables were significantly worse at the time of a flare compared to assessments when there was no flare. However, the variance was great and the differences, albeit statistically significant, were small. Notably, there was no significant difference between the serum urate at the time of a flare or at other times. To examine this in greater detail, we assessed each clinical variable at the time of flares in the 26 subjects who met criteria of remission and experienced flares. As can be seen in **Figure 3**, PGA for example, varied widely at the times of flares in these subjects. **Table 1** shows correlations between all components of remission and other clinical features in the 29 responders meeting criteria of "remission". Results of this analysis indicated weak or absent correlations among many of these variables. The highest correlation noted was between the two pain assessments (r=0.79), whereas the association between pain and TJC was lower (r=0.32-0.34); and, the association between pain and SJC was even less (r=0.16-0.23). Even the association between pain and PGA was modest (r=0.45-0.49). These results indicate that the components of the "remission" criteria may not all be improving contemporaneously in subjects with chronic or advanced gout and that other sets of characteristics may be more effective at defining a state of disease quiescence.

Results of Mixed Modelling

To develop new composite criteria for a CR from this data set, repeated measures, mixed effects modelling with backward elimination of components with the least statistical significance was carried out. Since gout is a chronic disease with a genetic predisposition and a biochemical underpinning, the new composite outcome measure determined from mixed modelling was considered to be a CR rather than "remission." Final criteria for CR were: serum urate <6 mg/dL, resolution of all measured tophi, PGA ≤1, SJC ≤1, and TJC ≤1.

Achievement and Maintenance of CR

The time to achieve a CR for all 34 responders is shown in **Figure 4A.** Of the 32 responders, 23 (71.9%) met the criteria of a CR. The time for 50% of patients to achieve a CR was 346 days. All patients who achieved a CR maintained it until the end of follow-up. The mean duration of CR was 507.4 days. There was a significant inverse relationship between the time to CR and the duration of the response (P=0.0008), **Figure 4B.**

Analysis of Results for Patients Who Responded to Administration of Monthly Pegloticase

The additional analysis of 25 patients who responded to administration of pegloticase every 4 weeks and completed the RCTs indicated that 16 (64%) met the criteria for a CR and that 50% of this subgroup achieved this response in 424 days (**Figure 5**).

DISCUSSION

We report herein, the first effort to validate the proposed remission criteria in gout, using a dataset from a therapeutic intervention. The proposed criteria for remission had been developed by Delphi consensus exercises, but had not been tested using a dataset from a randomized clinical trial.[20] This post-hoc evaluation indicated that 85.3% of responders to biweekly pegloticase met the criteria for remission, which included serum urate <6 mg/dL, no tophi, no flares, pain <2 on a 10 cm visual analog scale, and PGA <2 on a 10 cm visual analog scale. These criteria were assessed at each clinic visit by an independent evaluator who reviewed the individual patient records and all 5 criteria were required to be present contemporaneously for the subject to be considered as meeting the criteria of remission. Importantly, the clinical components of the criteria (omitting serum urate) could also distinguish between those with persistent lowering of serum urate (responders) and those without persistent urate lowering (non-responders) to the study medication and also between treated subjects and those receiving placebo.

Therefore, the proposed remission criteria clearly appeared to be effective in distinguishing the quality of the response in subjects with chronic refractory gout treated with pegloticase. Notably however, there was modest or no correlation between many components of the remission criteria. This suggested that the remission criteria were not ideal in assessing the quality of responses in chronic or advanced gout and that an alternative model might be more effective. Using a repeated effects mixed model with backward elimination, criteria for a CR in chronic or advanced gout were developed. Using these criteria, the vast majority of individuals (71.9%) with chronic or advanced gout treated with pegloticase who achieved persistently lower serum urate levels, reached criteria for CR; 50% of pegloticase-treated patients achieved CR in 11.5 months. The results from the subjects in the RCTs who responded to treatment with intravenous pegloticase administered every 2 weeks were validated with a second independent analysis of clinical results of patients treated with monthly intravenous pegloticase who met the response criteria in the RCT; 64% of these patients met the criteria for a CR with 50% achieving this response in 424 days. Although this validation exercise is not ideal because these subjects were part of the same RCTs that were used to generate the CR criteria, few other clinical trial data sets are available with sufficient clinical impact to assess the induction of a CR.

Although optimistically biased, the results from the monthly pegloticase cohort are intriguing because they suggest that fewer subjects in the monthly pegloticase treatment group achieve a CR and that it takes a longer period of treatment than was determined in the group receiving biweekly pegloticase, a result suggested in the RCTs, in which monthly pegloticase was less effective.[21] All of these results support the view that a composite index to determine a CR could be useful in a treat to target strategy.

It should be noted that the Delphi exercise[20] and the present study are not the only efforts to develop a composite measure of disease control in patients with gout. In one retrospective chart review, disease control for patients with gout was defined as a 12-month average serum urate ≤6 mg/dL, no flares, and no tophi, three of the five criteria in the proposed remission criteria; and it was noted that only 11% of 858 patients whose records were evaluated achieved this goal.[24] The Outcomes in Rheumatology Clinical

Trials (OMERACT) also endorsed specific domains that should be assessed in clinical trials of therapies for chronic gout and corresponding instruments for their measurement.[25] Based on OMERACT core domains and Delphi exercises, the GAS was developed. The first candidate GAS included seven indicators: 1) 12-month flare count; 2) serum urate; 3) pain (VAS); 4) VAS global activity assessment; 5) SJC; 6) TJC; and 7) cumulative measure of tophi. A second iteration included flares, serum urate, patient global assessment and the number of tophi. This final GAS demonstrated a good correlation with functional disability (criterion validity) and discrimination between patient- and physician-reported measures of active disease (construct validity).[17] In comparing different response criteria, it should be noted that those selected on the basis of the analysis carried out in the present study were the first set to be derived from data in a clinical trial, to clearly show responsiveness to change and to focus on chronic or advanced gout.

The present results, particularly the weak relationship between the occurrence of flares and other response measures in the patients who achieved remission, challenge the utility of this outcome. The findings that there were modest or absent correlations between many of the clinical characteristics and that there was wide variation in clinical features at the time of a flare support the results of the repeated measures, mixed effects modelling that did not include absence of flares in the criteria for a CR. The lack of a strong relationship between flares and other clinical characteristics should not be taken as evidence that flares are unimportant in patients with gout. This view is supported by results for all patients who received pegloticase every 2 weeks which showed that tender and swollen joint counts, pain, and PGA were all significantly worse near the times of flares vs times when flares had not occurred. The absence of a relationship between flares and other variables and the high variability in PGA scores at the time of flares in patients who met the criteria for remission may be related to the very broad definition of flares in these studies, which was "self-reported acute joint pain and swelling requiring treatment".[21] A more rigorous flare definition, such as the one recently proposed by Gaffo et al. (i.e., presence of ≥ 3 out of 4 criteria: 1) patient-defined gout flare, 2) pain at rest >3 on a 0-10 numeric rating scale, 3) presence of at least one swollen joint, and 4) presence of at least one warm joint) may be more suitable for use in future studies of gout treatment and could result in flares being included in CR criteria.[26]

It has been noted that when establishing treatment targets, clinicians should consider outcomes most important to patients[27], and results from one analysis have suggested that development of a composite outcome may be difficult from this perspective. Results from a study in which three patient groups rated the importance of different outcomes, indicated that the relative importance accorded to each outcome domain was different across the groups. Both the presence of tophi and pain between flares were ranked as less important, whereas gout flares were ranked as more important and the relative importance of serum urate and activity limitations was variable.[27] The relatively low importance of tophi to patients in this study is surprising since an assessment of 110

patients with severe “treatment failure” gout showed that the presence of tophi was associated with significantly worse bodily pain, general health, role-physical, social functioning, vitality, and Physical Component Score as measured by the SF-36.[28] However, another analysis indicated that frequency of flares and severity and duration of pain, but not serum urate or the presence of tophi and the number of joints involved in a typical flare, significantly impacted the patient's quality of life.[29] The development of evidence-based criteria for CR may provide the basis for future examination of the relationship between patient expectations and results of clinical trials and provide more effective goals for a treat- to-target strategy.

There are limitations to this study. First, the data were derived from two identical RCTs with an OLE and will require confirmation with other data sets. Secondly, as mentioned above, the results of the validation exercise for the CR criteria were likely to be optimistically biased as they were obtained from a cohort of the same RCTs used to generate the composite measure. Finally, this analysis was carried out in a group of subjects with advanced gout who met entry criteria for a clinical trial of subjects with chronic refractory gout. Whether the proposed criteria will be useful in subjects with less advanced gout remains to be determined. Regardless, the data provide a first step in validating the proposed criteria for remission in gout and suggest an additional evidenced-based set of criteria to identify subjects with a CR.

In conclusion, the present study employed clinical trial data to validate the proposed gout remission criteria and also to define criteria that tended to track together more than the components of the remission criteria. This composite complete responder measure can serve as an evidence-based target to inform the design and endpoints of future urate lowering therapy trials in chronic gout.

AUTHOR CONTRIBUTION

All authors had full access to the study data, contributed to the writing and review of the manuscript and approved the final version for publication.

COMPETING INTERESTS

N. Schlesinger reports research grants from Pfizer and Amgen; consulting fees from Novartis, Horizon Pharma, Selecta Biosciences, Olatec, IFM Therapeutics, and Mallinckrodt Pharmaceuticals.

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A.E. Yeo reports contractor fees from Horizon Pharma.

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Tables

Table 1. Correlations between all components of remission and other clinical features in the 29 serum urate responders meeting criteria of “remission”.

SF-36 pain	VAS pain	SJC	TJC	PGA	Tophus Category	Variable
-0.34787	0.22553	-0.09753	0.00727	0.13198	0.00523	**Serum urate**
<.0001	0.0004	0.0854	0.8982	0.0201	0.9493	**P-value**
	-0.79152	-0.23102	-0.34343	-0.49247	-0.13874	**SF-36 pain**
	<0.0001	0.0006	<0.0001	<0.0001	0.0915	**P-value**
		0.15509	0.32799	0.45337	0.20606	**VAS pain**
		0.0226	<0.0001	<0.0001	0.0123	**P-value**
			0.55837	0.57825	-0.04911	**SJC**
Tophus Category			<0.0001	<0.0001	0.5506	**P-value**
Progressive disease = 2				0.63261	0.0923	**TJC**
Stable disease = 3				<0.0001	0.2613	**P-value**
Partial response = 4					0.0688	**PGA**
Complete response = 5					0.4028	**P-value**

Figure Legends

Figure 1A-B. Time to achieve criteria of "remission" in **A.** Entire group of subjects treated with biweekly pegloticase **B.** Subjects meeting the criteria of responder and having persistent urate lowering. The two lines in **B** represent data from the entire responder cohort (n=32) and those who met criteria for remission (n=27)

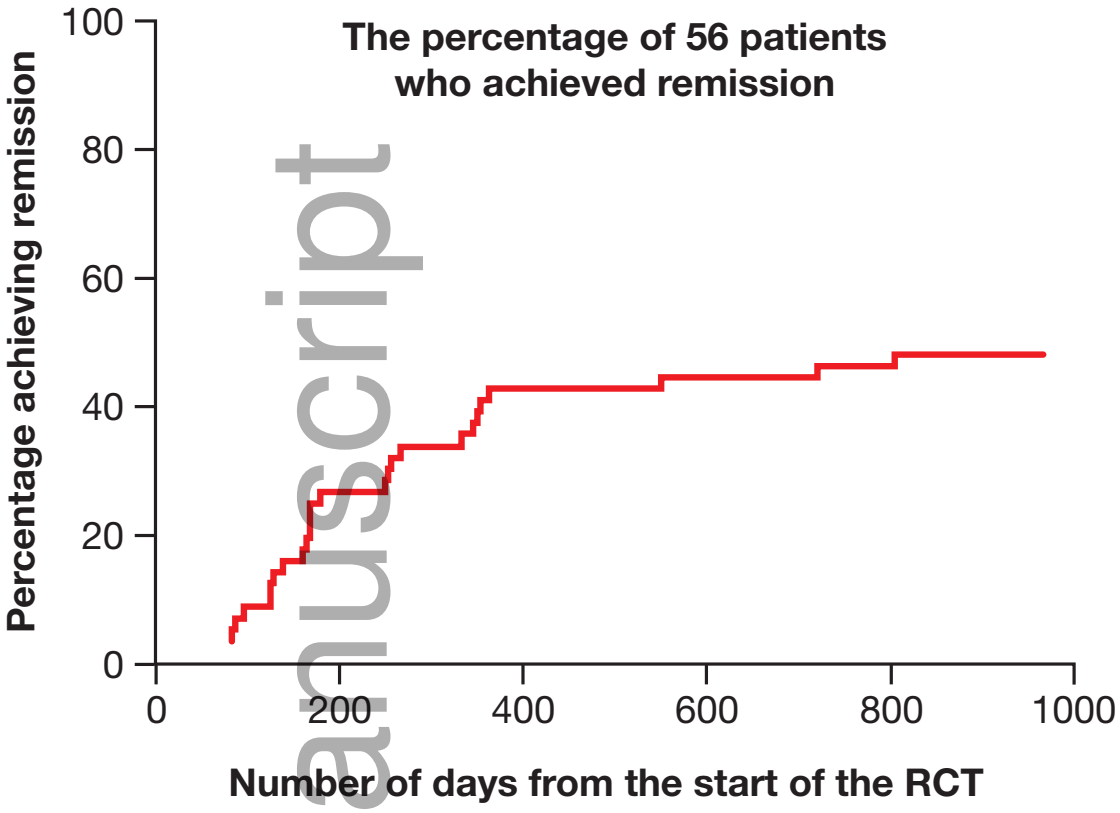
Figure 2. Mean values (+ standard deviations [SD]) for clinical measures taken at clinical visits that were or were not associated with flares. Results are for all patients (n=56) treated with pegloticase every 2 weeks in the RCTs and OLE. There were 147 observations associated with flares and 201 observations not associated with flares

Figure 3. Values for PGA at the time of flares for q2w responders who met the criteria for remission

Figure 4. **A.** Time to CR (sUA responders in RCTs)
B. Relationship between time to achieve CR and duration of response

Figure 5. Time to CR for patients who responded to administration of pegloticase every 4 weeks; CR was achieved by 16 (64%) of 24 patients with 50% achieving this response in 424 days

A



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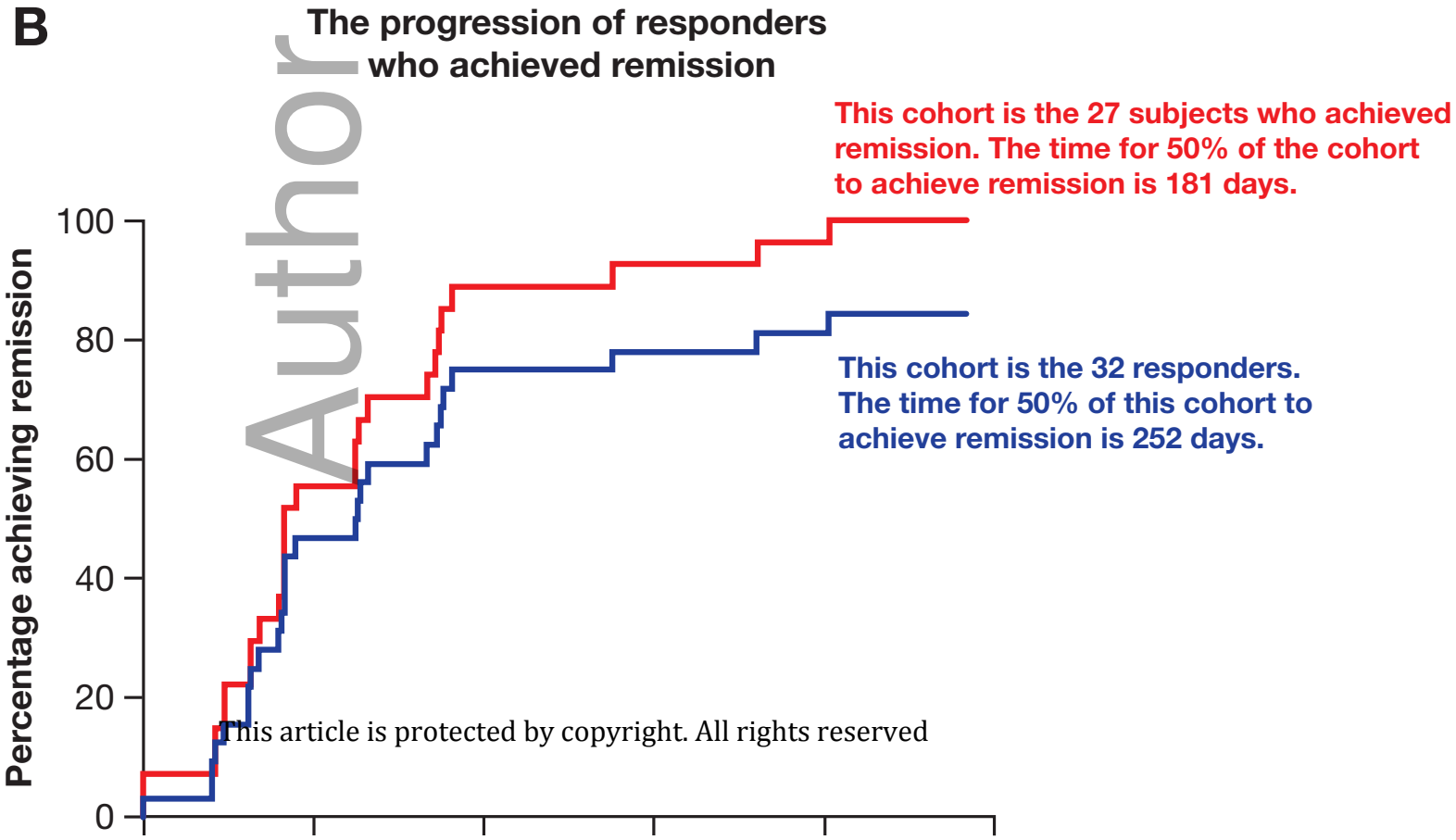

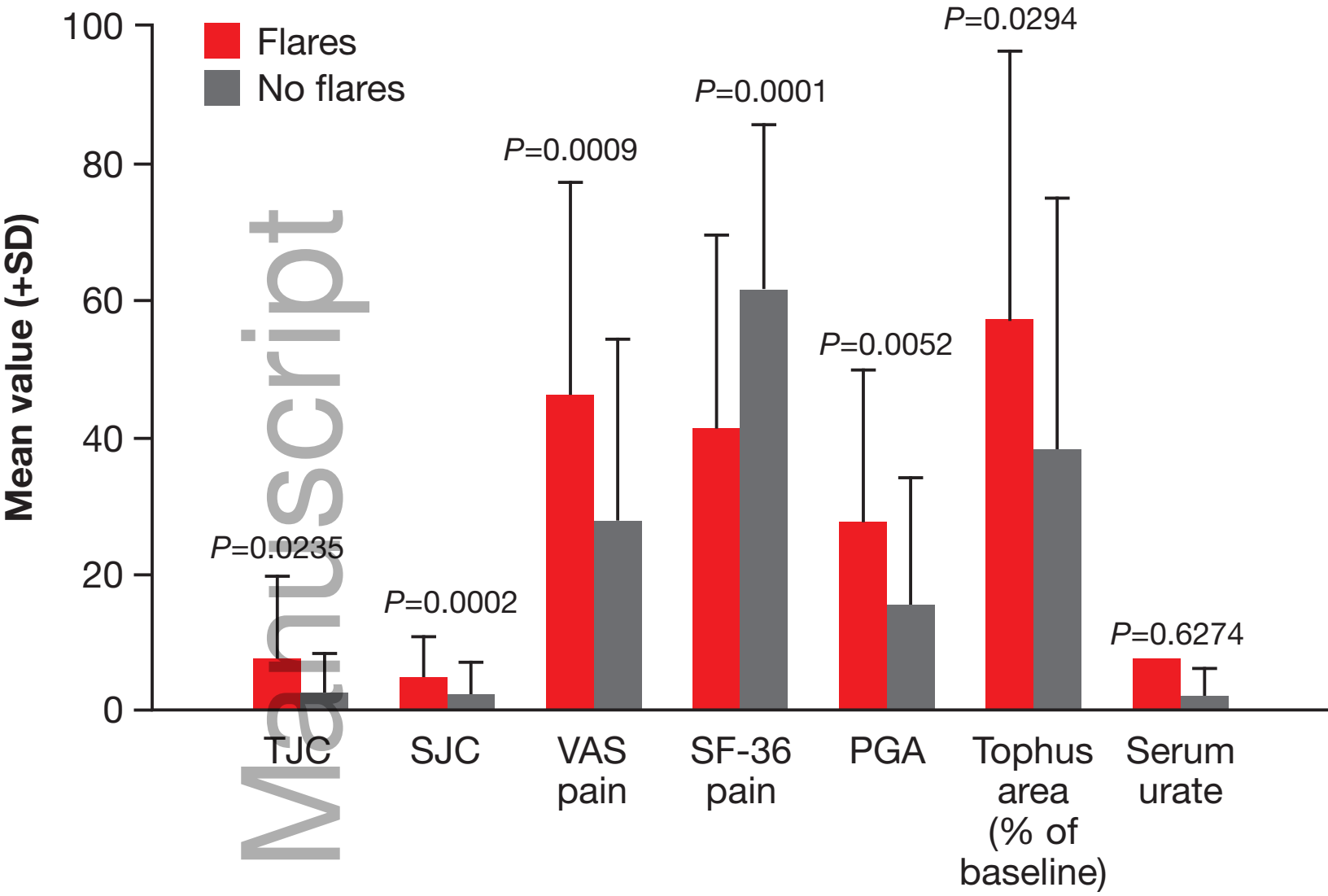

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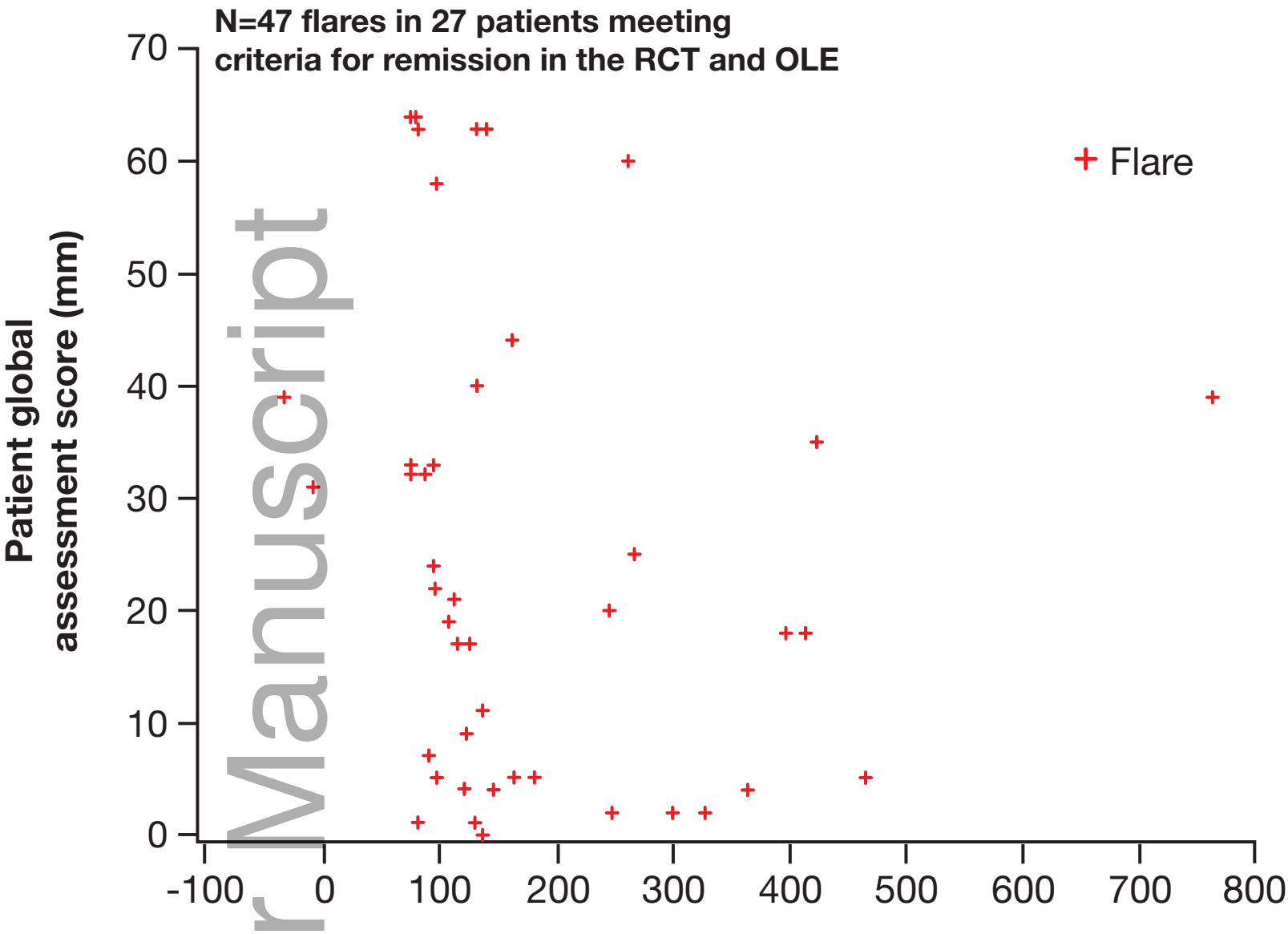

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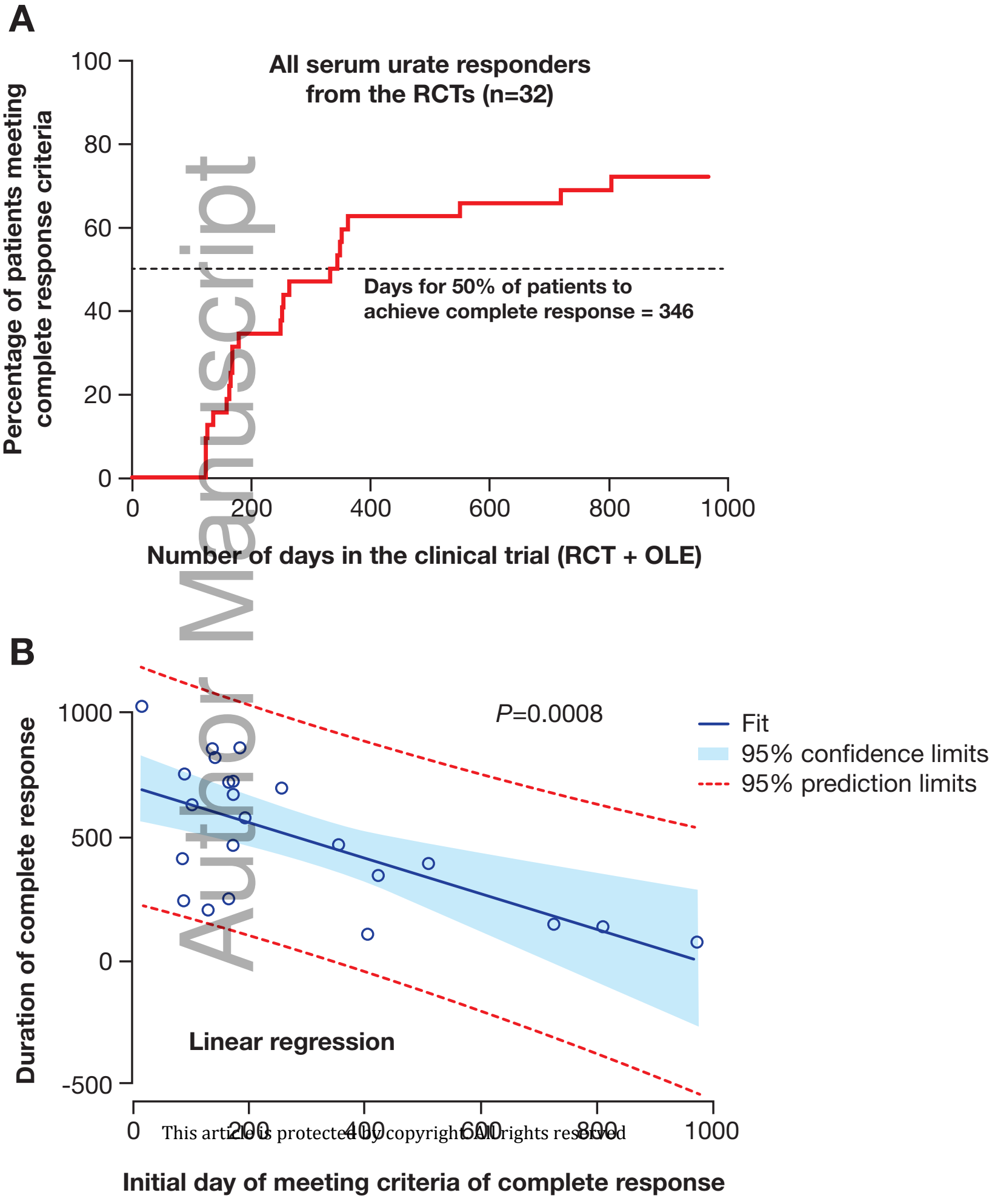

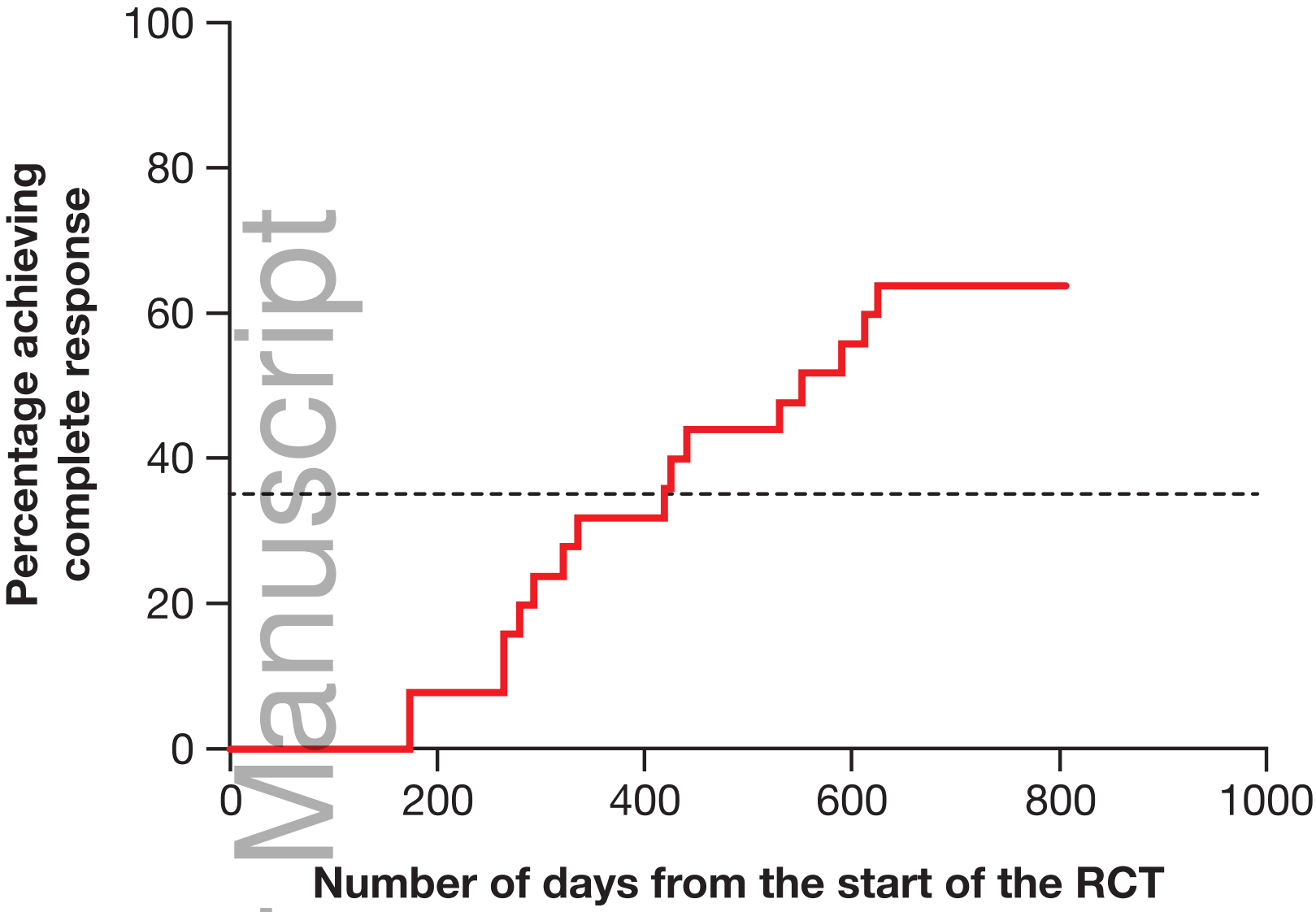

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