Supplemental Data

The supplemental data have been provided by the authors to give readers additional information about their work.

Supplement to M. Shima, H. Hanabusa, M. Taki, et al. Long-term safety and efficacy of emicizumab in a phase 1/2 study in hemophilia A patients with or without inhibitors.

Supplementary Appendix

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Supplemental Methods

Criteria for the extended administration starting dosage are as follows:

- For subjects in whom bleeding episodes required coagulation factor replacement therapy ≥50% less frequently in the phase 1 study (12 weeks) than in the six months before emicizumab treatment, extended treatment was started at the dose administered in the phase 1 study, or at the next dose up.
- For subjects in whom bleeding episodes required coagulation factor replacement therapy <50% less frequently in the phase 1 study (12 weeks) than in the six months before emicizumab treatment, extended treatment was started at the next dose up from that administered in the phase 1 study. However, treatment could not commence until the Efficacy and Safety Evaluation Committee approved escalation to the next dose.

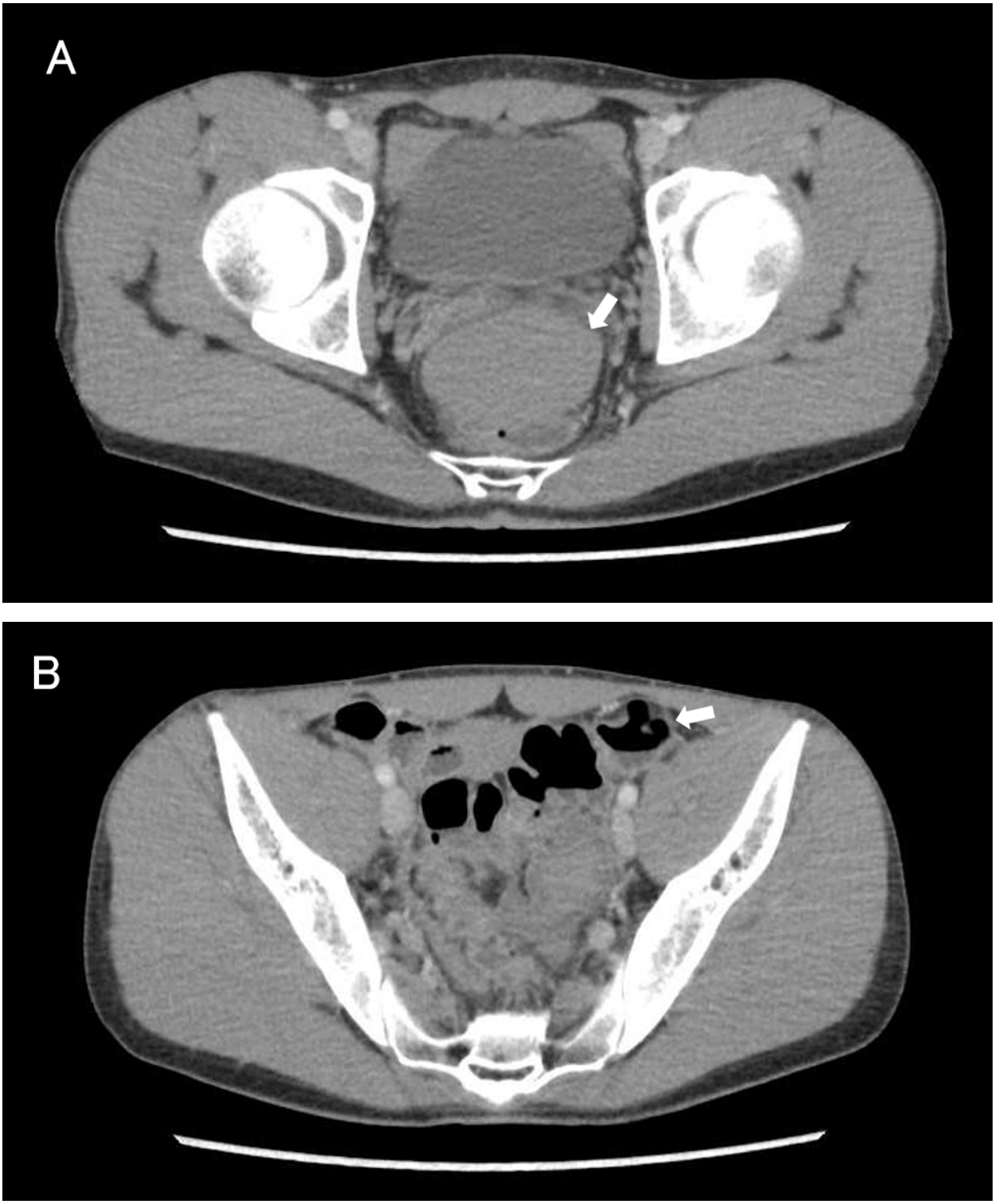
Supplemental Table S1. AEs related to emicizumab treatment

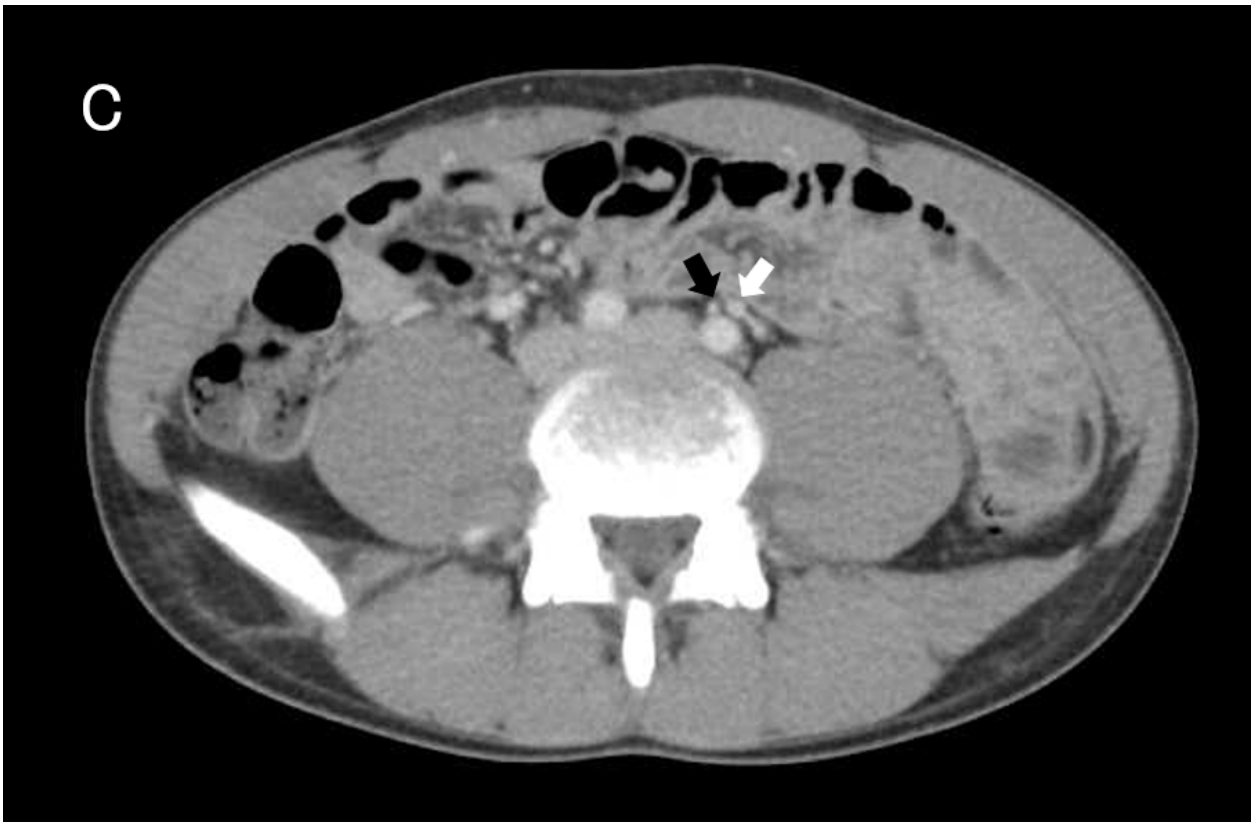
AE, n (%)	Patients (N = 18)
Total patients with at least 1 related AE	7 (39.0)
Total number of related AEs	14
Injection-site AEs	
Injection-site erythema	3 (16.7)
Injection-site pruritus	3 (16.7)
Injection-site discomfort	1 (5.6)
Injection-site pain	1 (5.6)
Injection-site rash	1 (5.6)
Malaise	1 (5.6)
Diarrhea	1 (5.6)
Nausea	1 (5.6)
Blood creatinine phosphokinase increased	1 (5.6)
C-reactive protein increased	1 (5.6)

All data collected following dose up-titrations were included.

AE, adverse event.

Supplemental Figure S1. Findings of contrast-enhanced abdominal computed tomography (CT) obtained on Day 477 at the diagnosis of hematoma



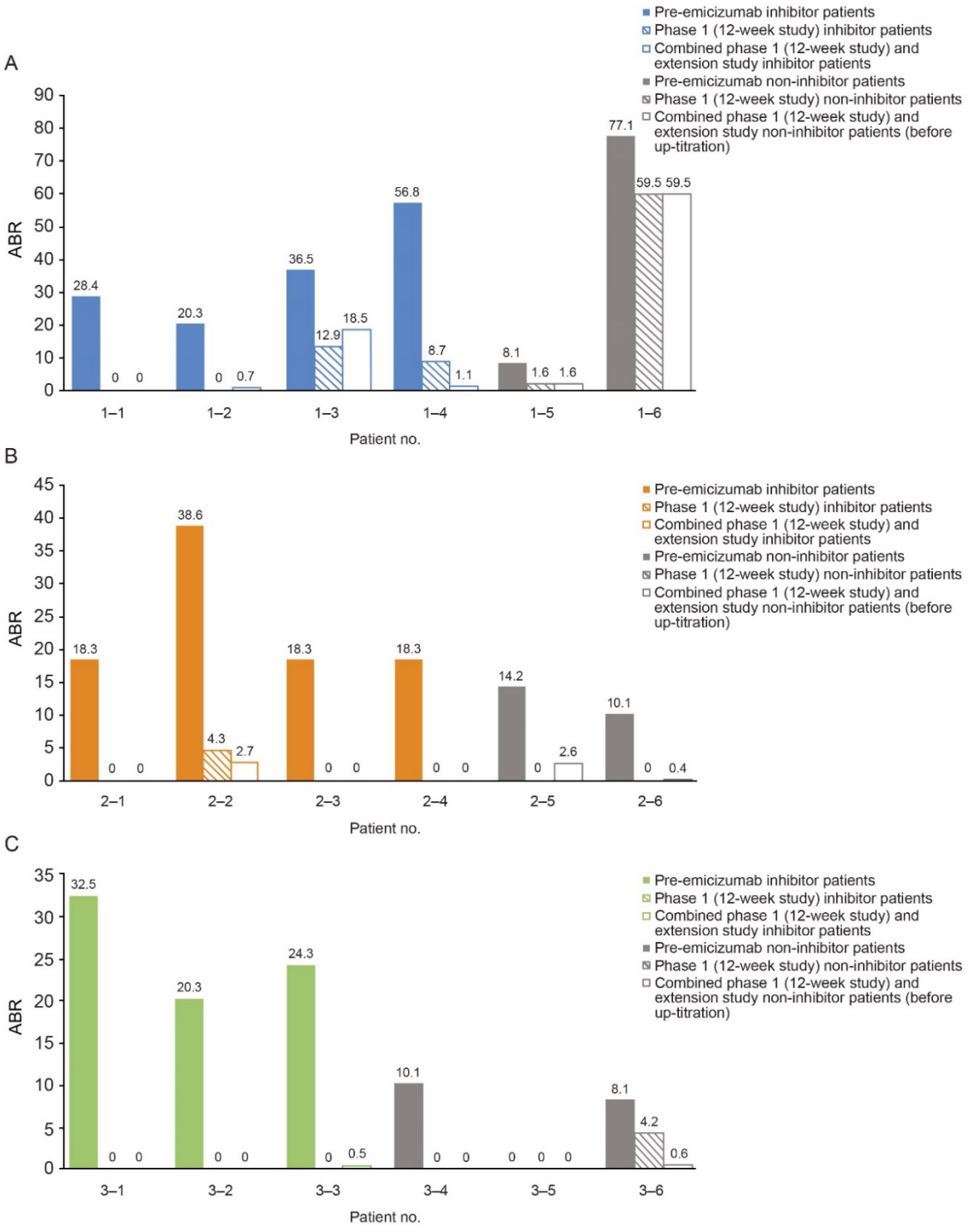


A. CT showed fluid collection in the pelvic cavity (maximum diameter 6.0 cm; arrow). CT value of fluid collection was as high as 62±12.3 (mean±SD), and a hematoma was diagnosed. There was no change before and after injection of contrast medium, which suggested that there was no active bleeding.

B. The intestinal wall was well enhanced with no thickening observed, which suggested no evidence of edema and ischemia (arrow).

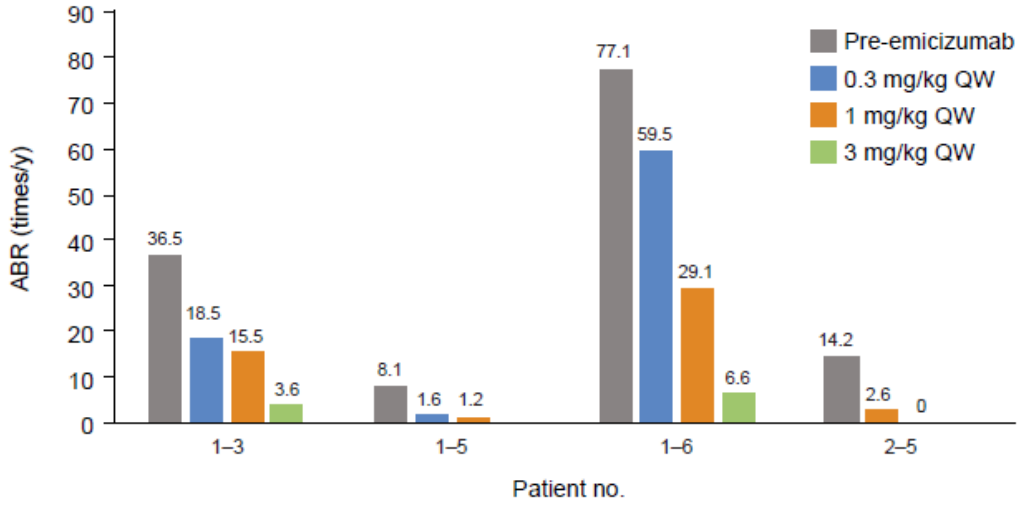
C. The inferior mesenteric artery (black arrow) and the inferior mesenteric vein (white arrow) were well enhanced with no obvious thrombus identified.

Supplemental Figure S2. Individual ABRs (any bleeding site) pre- and post-emicizumab for each patient with or without inhibitors. (A) Cohort 1. **(B)** Cohort 2. **(C)** Cohort 3.



All data collected following dose up-titrations were excluded; data before dose up-titration were used for ABR calculation of the combined phase 1 (12-week) and extension studies.

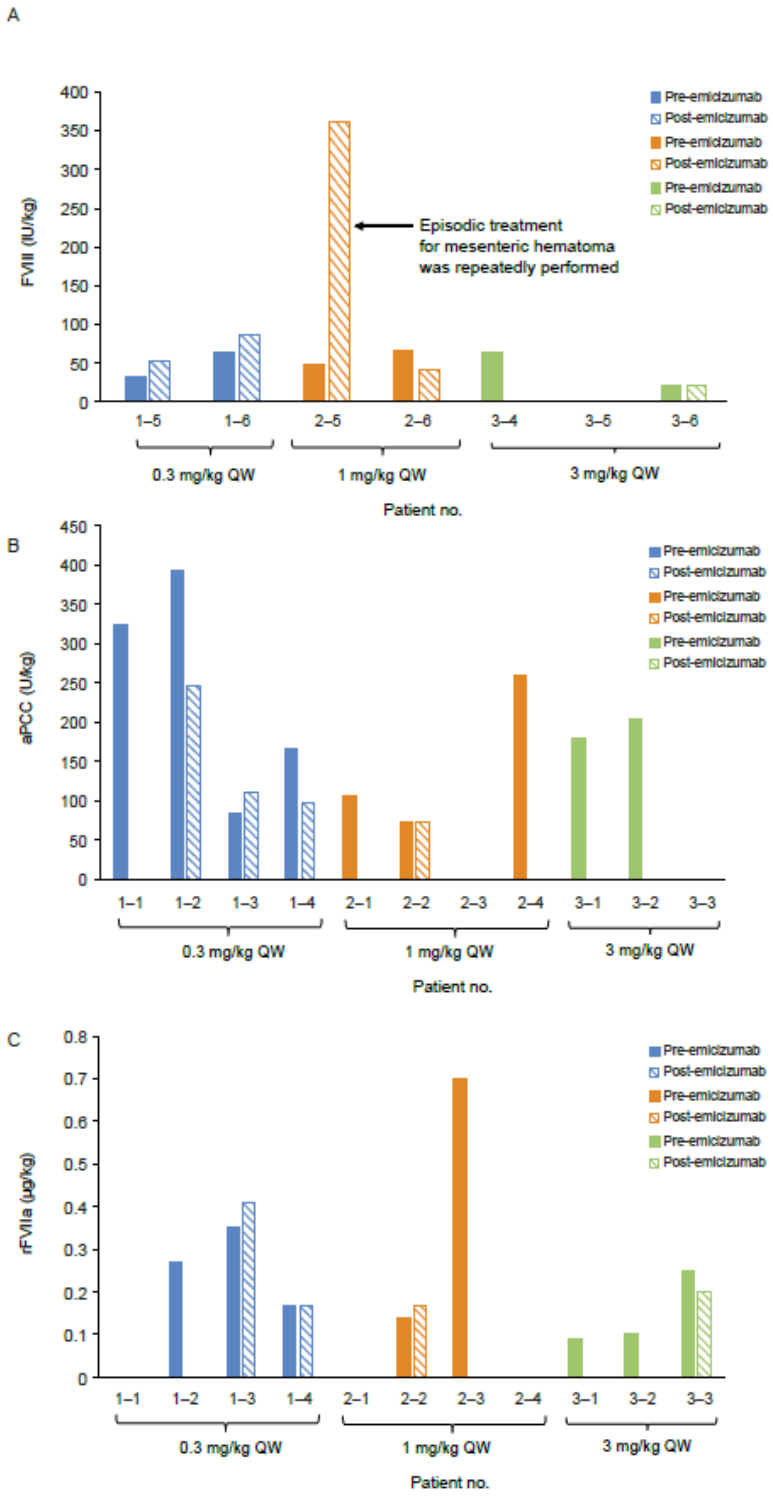
Supplemental Figure S3. Individual ABRs (any bleeding site) pre- and post-emicizumab for patients who had dose up-titration.



Dosing	Weeks to calculate ABR			
0.3 mg/kg QW	45	96	12	–
1 mg/kg QW	27	44	25	81
3 mg/kg QW	72	–	72	37

ABR, annualized bleeding rate; QW, once weekly.
ABRs for each given dose were calculated based on combined data from the phase 1 (12-week) and extension studies.

Supplemental Figure S4. Intra-patient mean amounts of coagulation factor required per bleeding event (any bleeding site) pre- and post-emicizumab for each patient. (A) FVIII. **(B)** aPCC. **(C)** rFVIIa.



All data collected following dose up-titrations were included. Emicizumab dose indicates the assigned dose for each patient's respective cohort in the 12-week study.