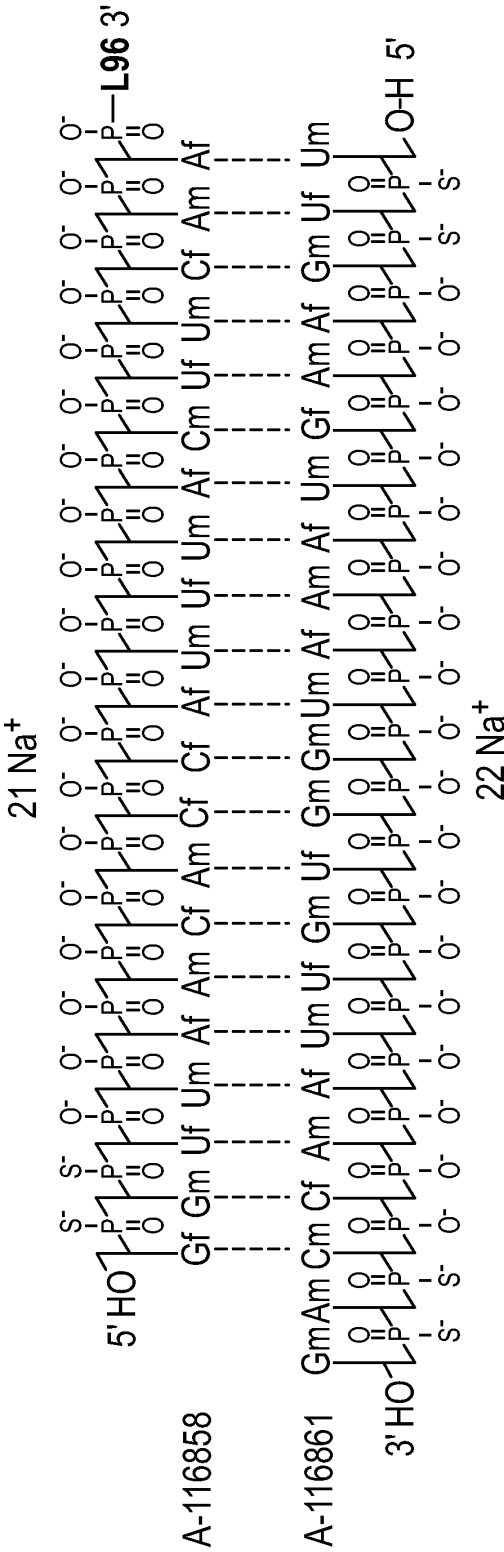




Af, Cf, Gf, Uf = 2'-F ribonucleosides
Am, Cm, Gm, Um = 2'-OMe ribonucleosides

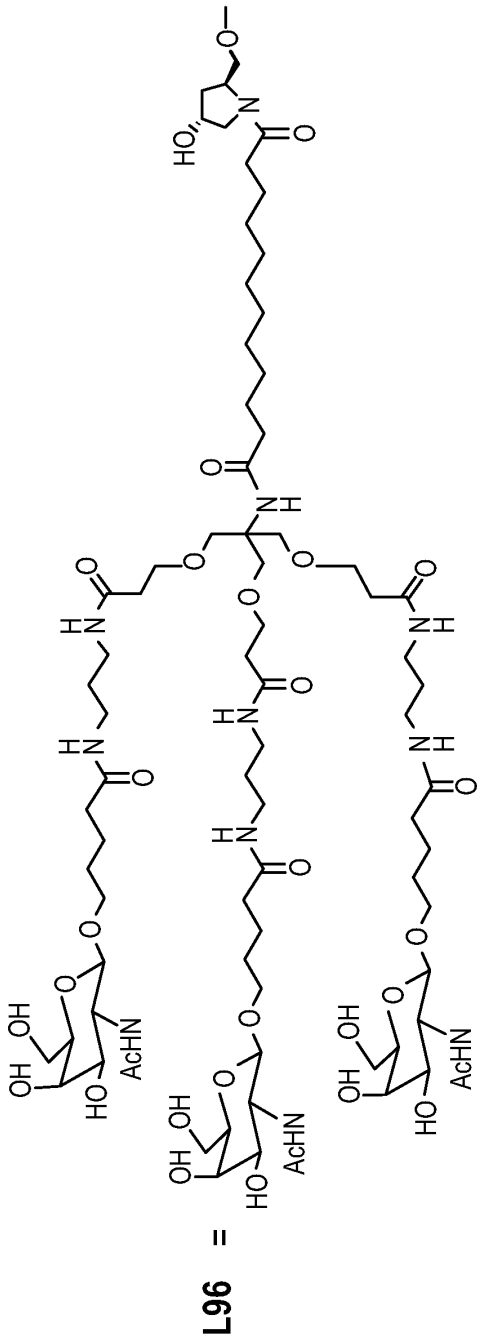


FIG. 1

Molecular formula and molecular mass			
	Fitusiran (Duplex)	A-116858 (Sense strand)	A-116861 (Antisense strand)
Molecular formula sodium salt	C ₅₂₀ H ₆₃₆ F ₂₁ N ₁₇₅ Na ₄₃ O ₃₀₉ P ₄₃ S ₆	C ₂₈₅ H ₃₆₉ F ₁₂ N ₈₅ Na ₂₁ O ₁₆₄ P ₂₁ S ₂	C ₂₃₅ H ₂₆₇ F ₉ N ₉₀ Na ₂₂ O ₁₄₅ P ₂₂ S ₄
Molecular formula free acid	C ₅₂₀ H ₆₇₉ F ₂₁ N ₁₇₅ O ₃₀₉ P ₄₃ S ₆	C ₂₈₅ H ₃₉₀ F ₁₂ N ₈₅ O ₁₆₄ P ₂₁ S ₂	C ₂₃₅ H ₂₈₉ F ₉ N ₉₀ O ₁₄₅ P ₂₂ S ₄
Molecular weight sodium salt	17,193 Da	9,035 Da	8,159 Da
Molecular weight free acid	16,248 Da	8,573 Da	7,675 Da

FIG. 1 (Continued)

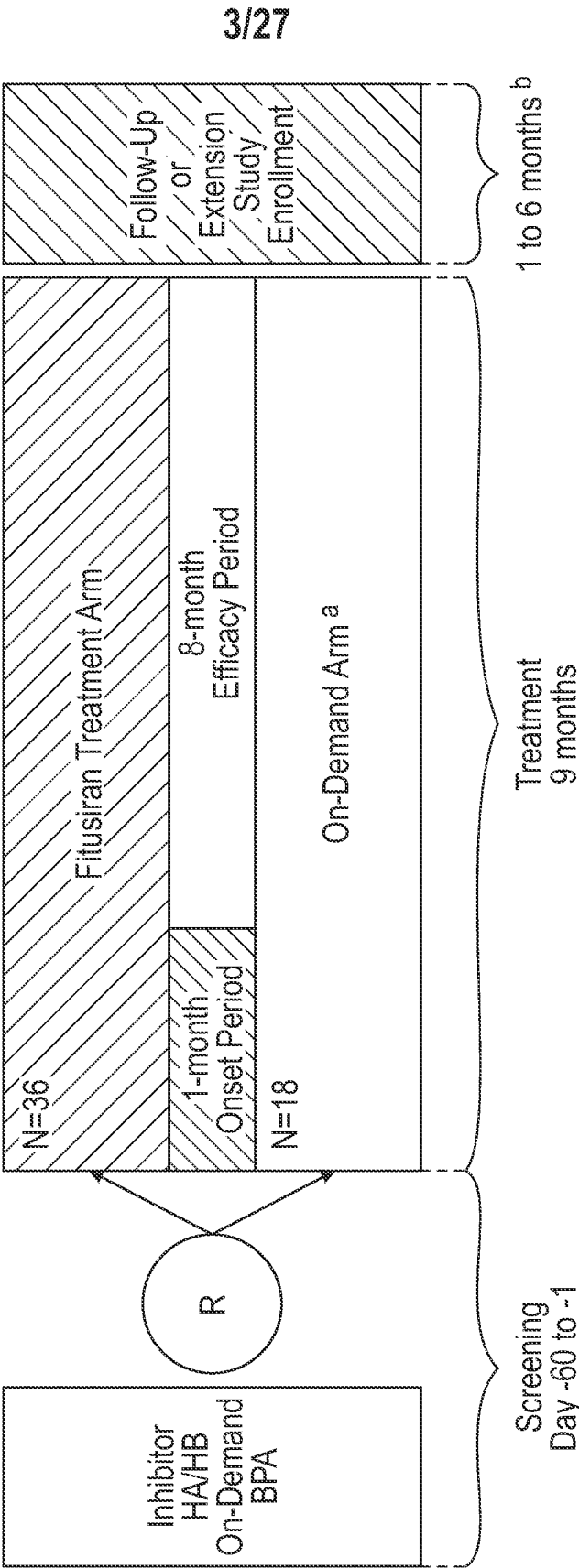


FIG. 2

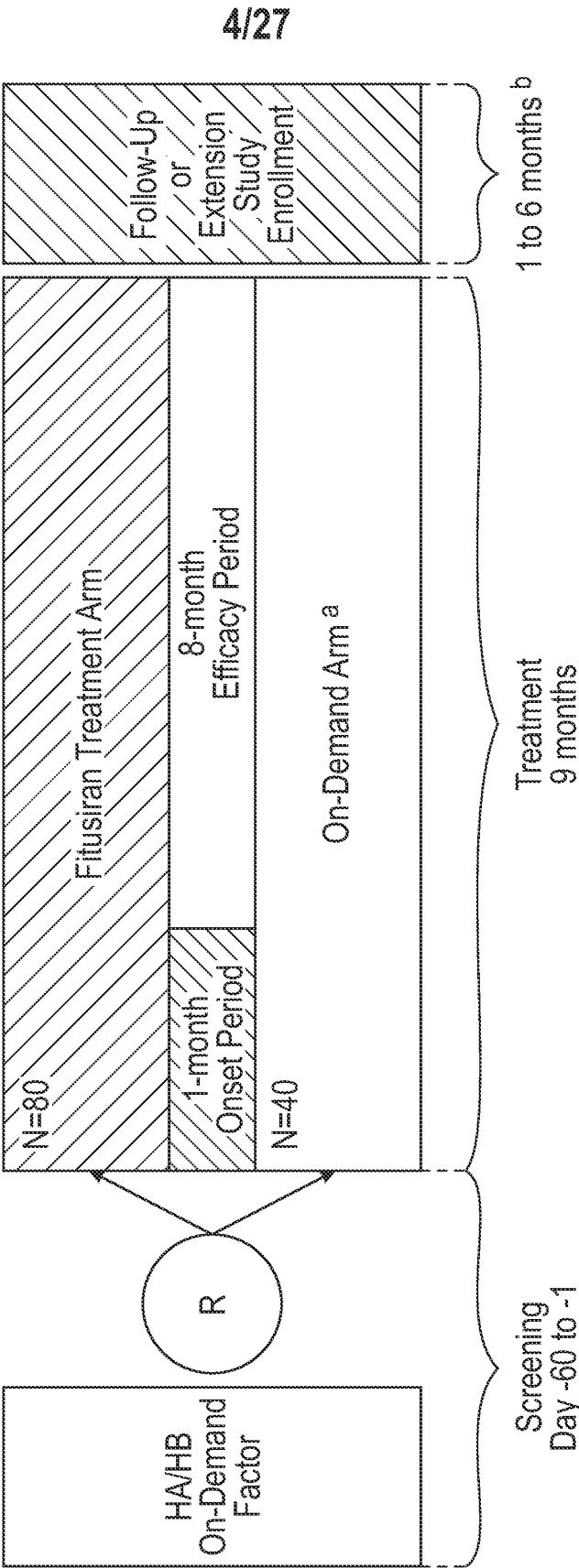


FIG. 3

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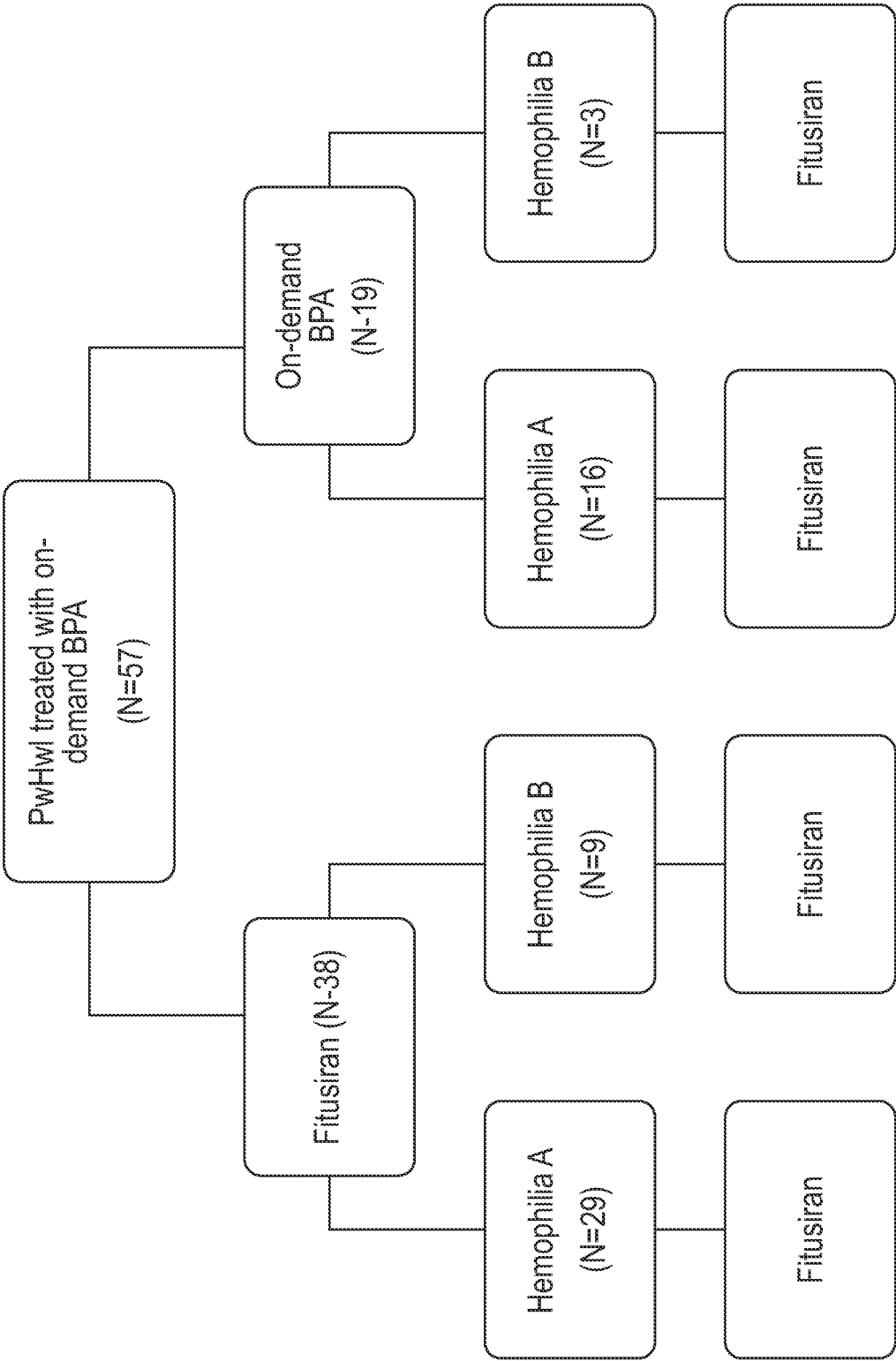


FIG. 4

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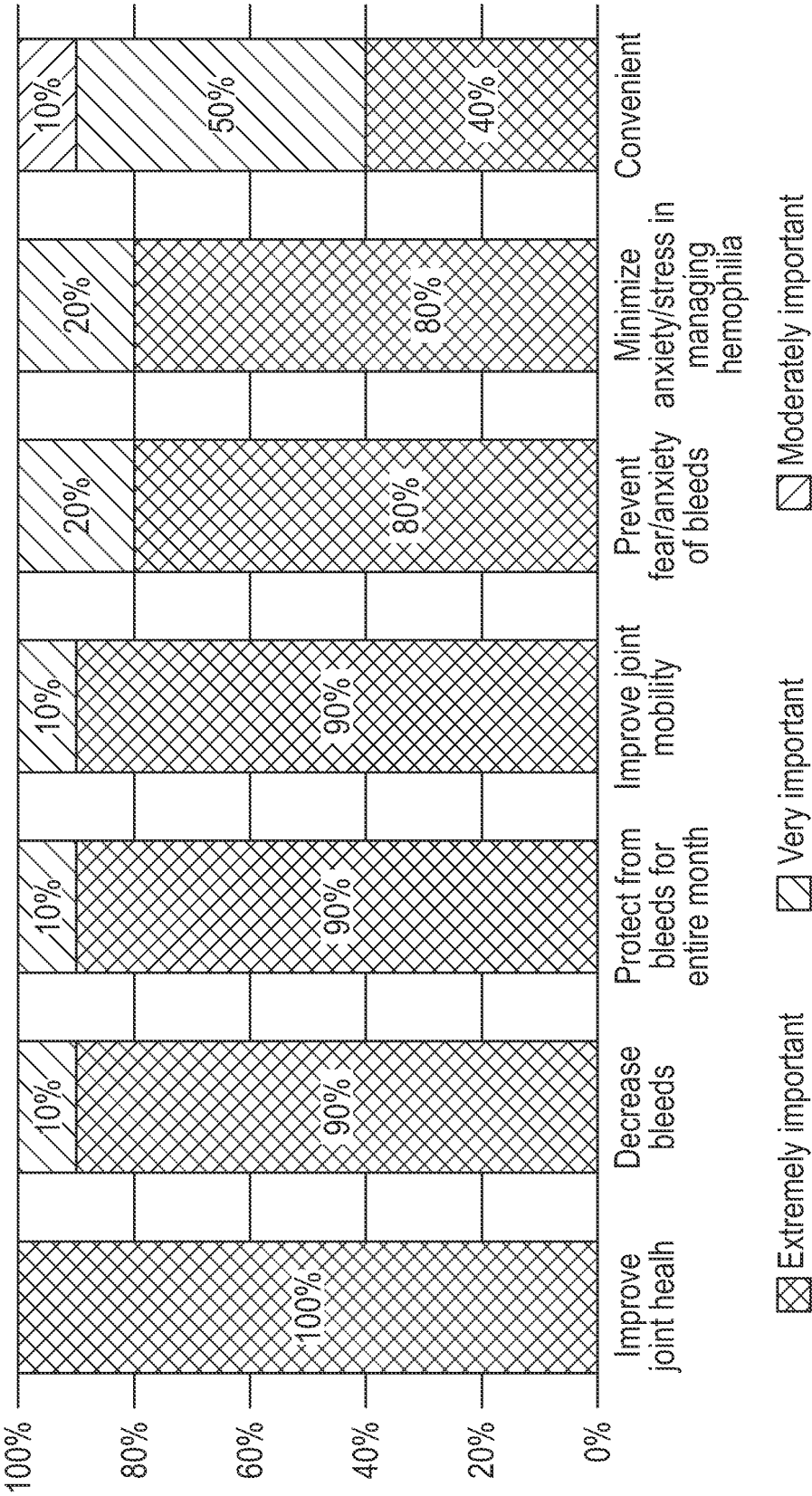


FIG. 5

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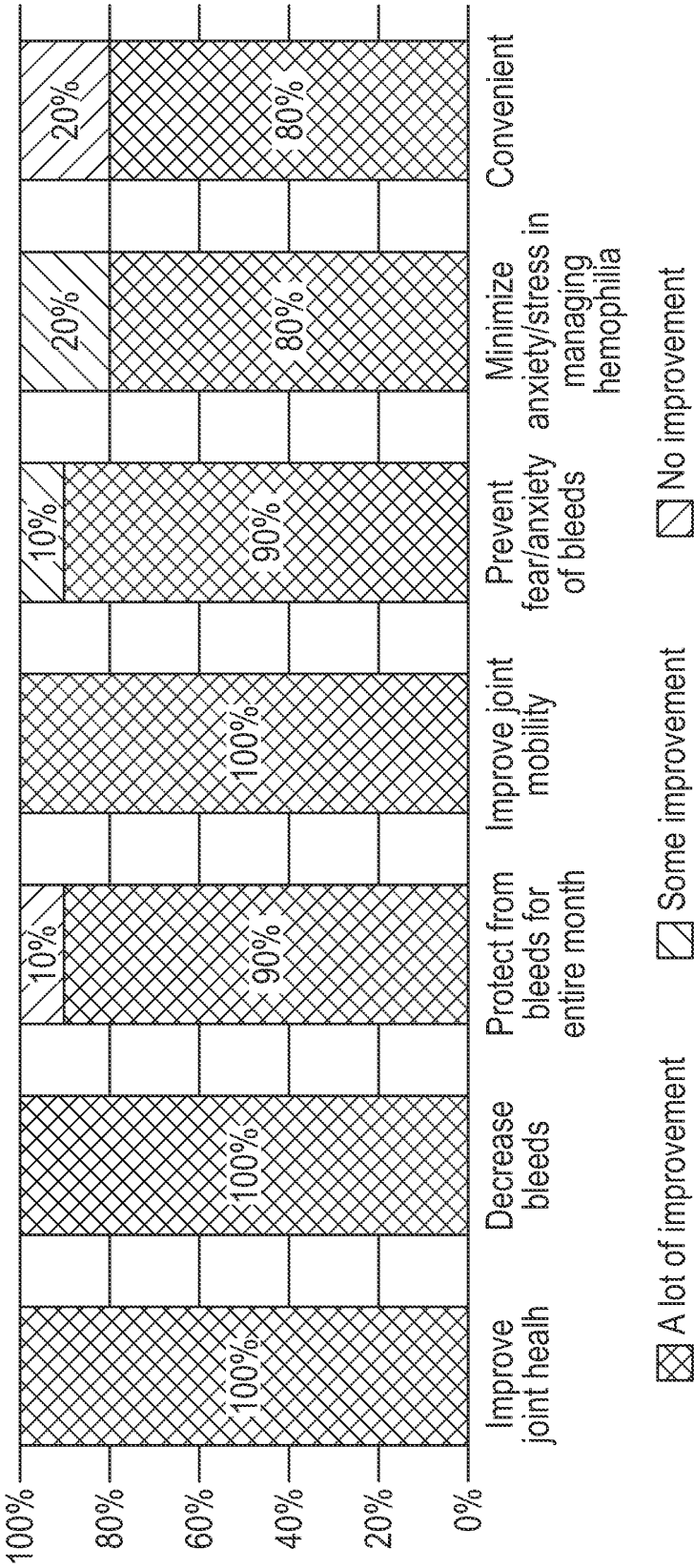
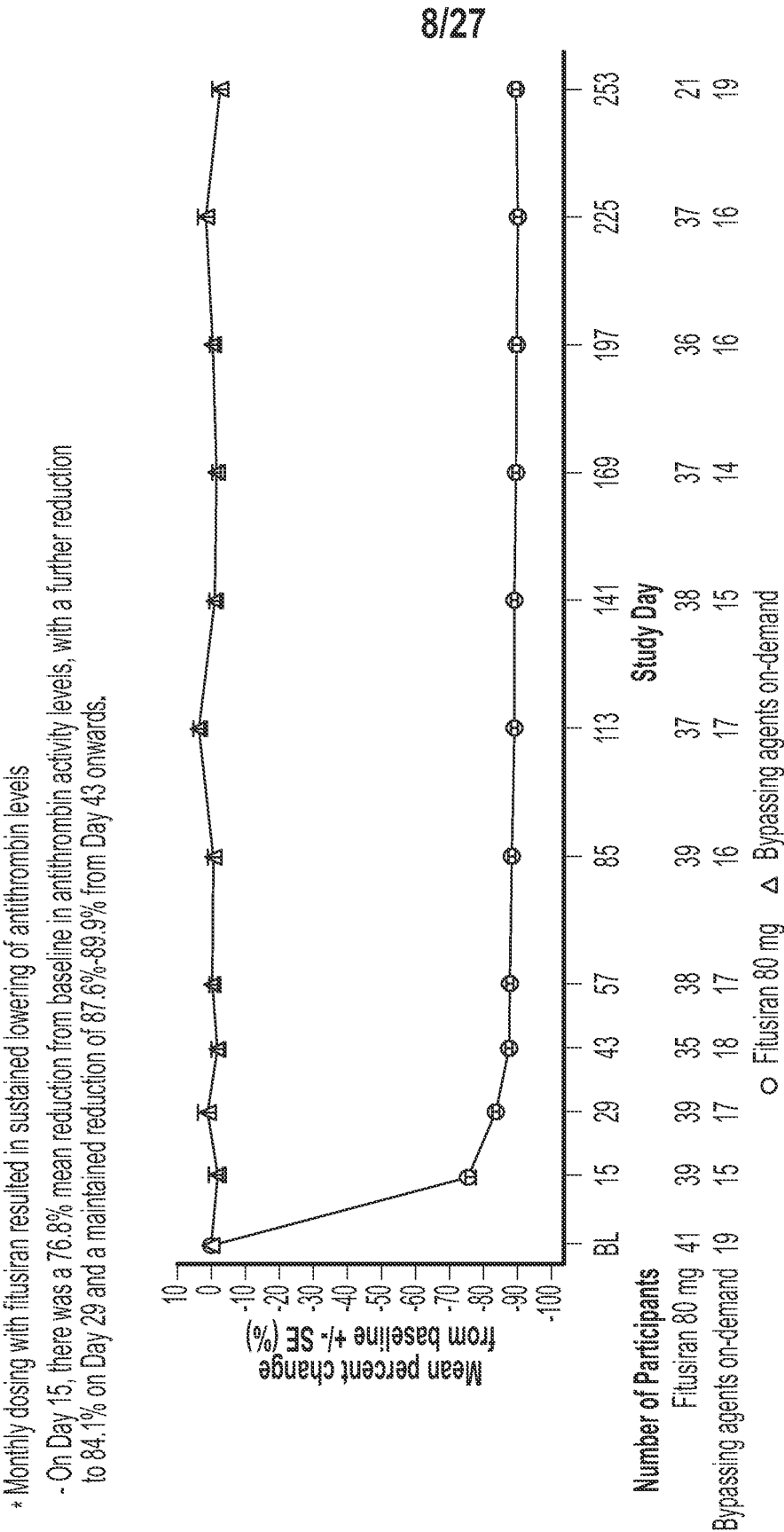


FIG. 6

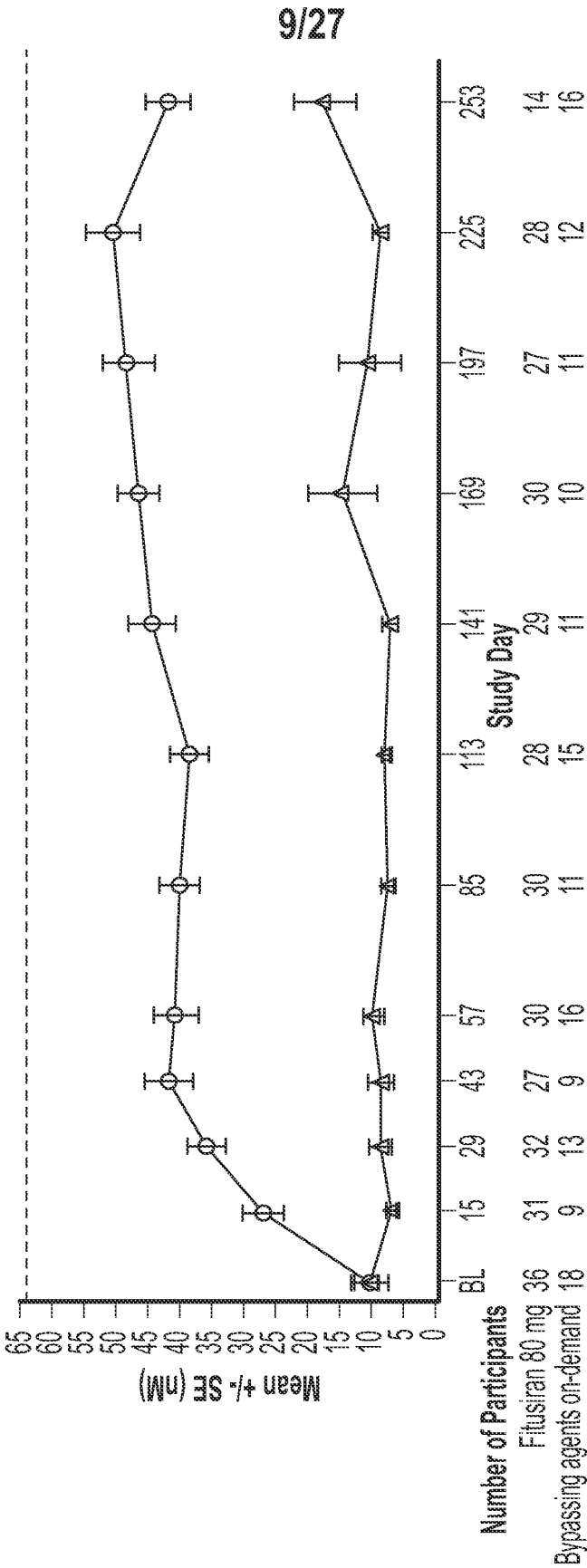


Measurements after fitusiran discontinuation +28 days were excluded. Measurements from start date of heparin, antithrombin concentrate and Factor Xa inhibitor to the final date on which those products were administered plus 5 half-lives of that specific product were excluded. Measurements in the period of missing at least two consecutive fitusiran doses were excluded. Only central laboratory assessments were taken into account. BL, baseline; GE, standard error.

FIG. 7

* Consistent with the mechanism of action of fitusiran, thrombin generation increased with antithrombin lowering

- There was a mean increase in peak thrombin generation of 21.9 nM from baseline on Day 15, with a further increase to 30.8 nM on Day 29 and a maintained increase of 36.8-47.5 nM from Day 43 onwards
- Peak thrombin generation reached a mean of 46.67 nM by Day 43 (a 540% change from baseline) that remained elevated during the course of fitusiran treatment.



○ Fitusiran 80 mg ▲ Bypassing agents on-demand -- Lower level of peak thrombin generation in healthy volunteers (range 64-210 nM)

Measurements after fitusiran discontinuation +28 days were excluded. Measurements within 48 hours of factor, BPA or antifibrinolytic administration were excluded. Measurements without a corresponding ETP AUC value were deemed unreliable and excluded from analysis. Measurements from start date of heparin, antithrombin concentrate and Factor Xa inhibitor to the final date on which those products were administered plus 5 half-lives of that specific product were excluded. Measurements in the period of missing at least two consecutive fitusiran doses were excluded. Only central laboratory assessments were taken into account. BL, baseline; BPA, bypassing agents; ETP AUC, area under the curve of the endogenous thrombin potential; SE, standard error.

FIG. 8

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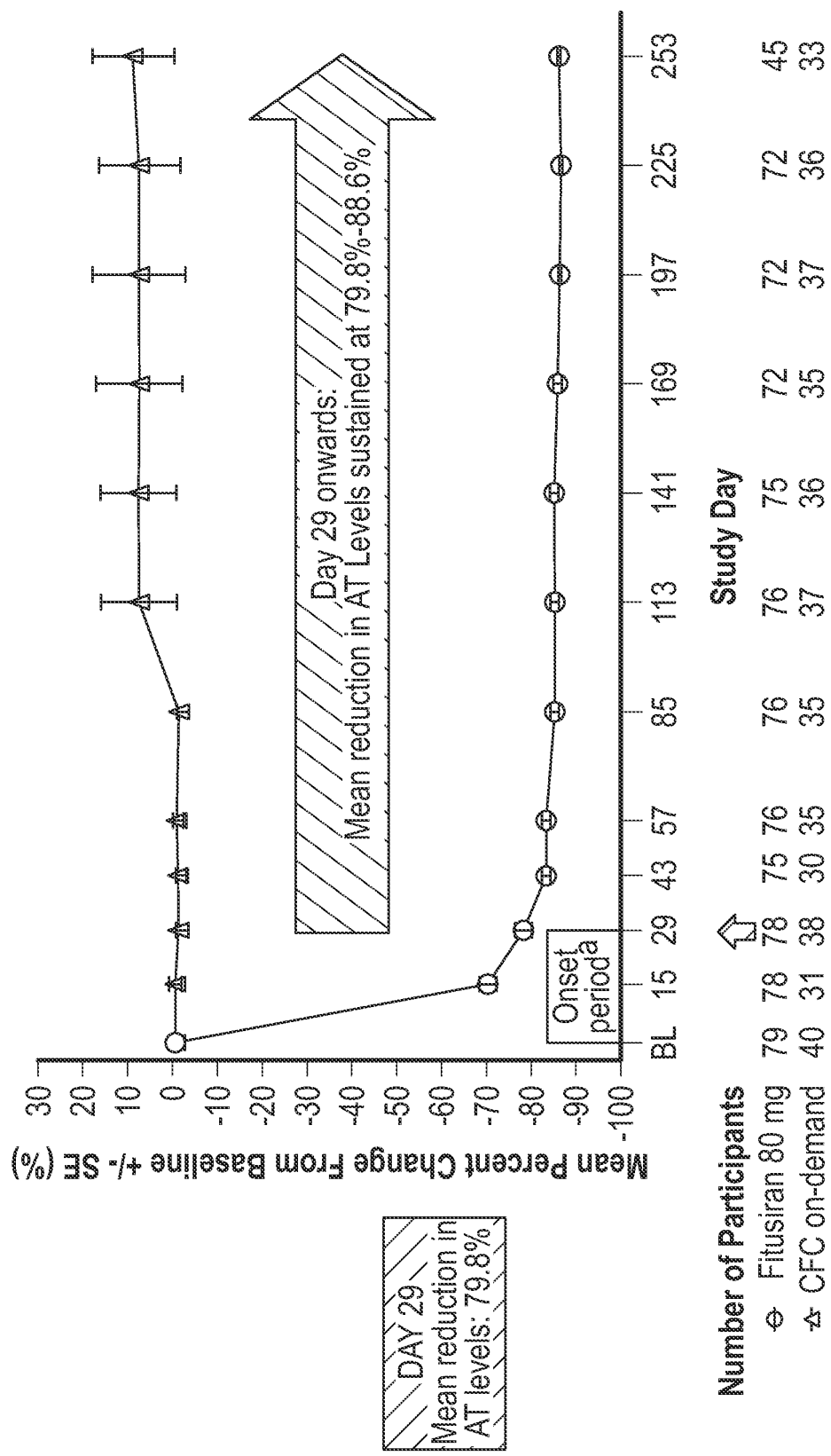


FIG. 9

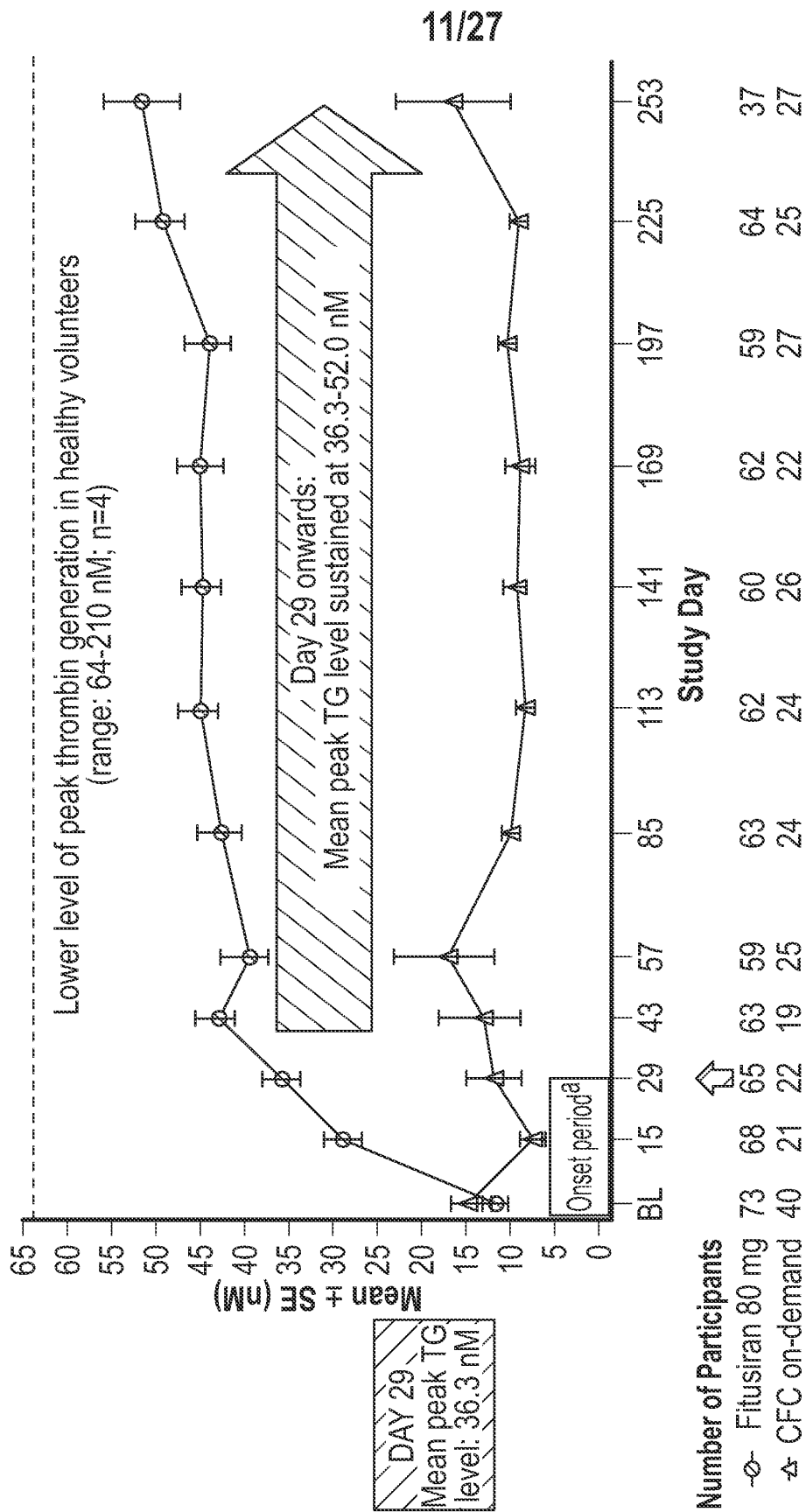


FIG. 10

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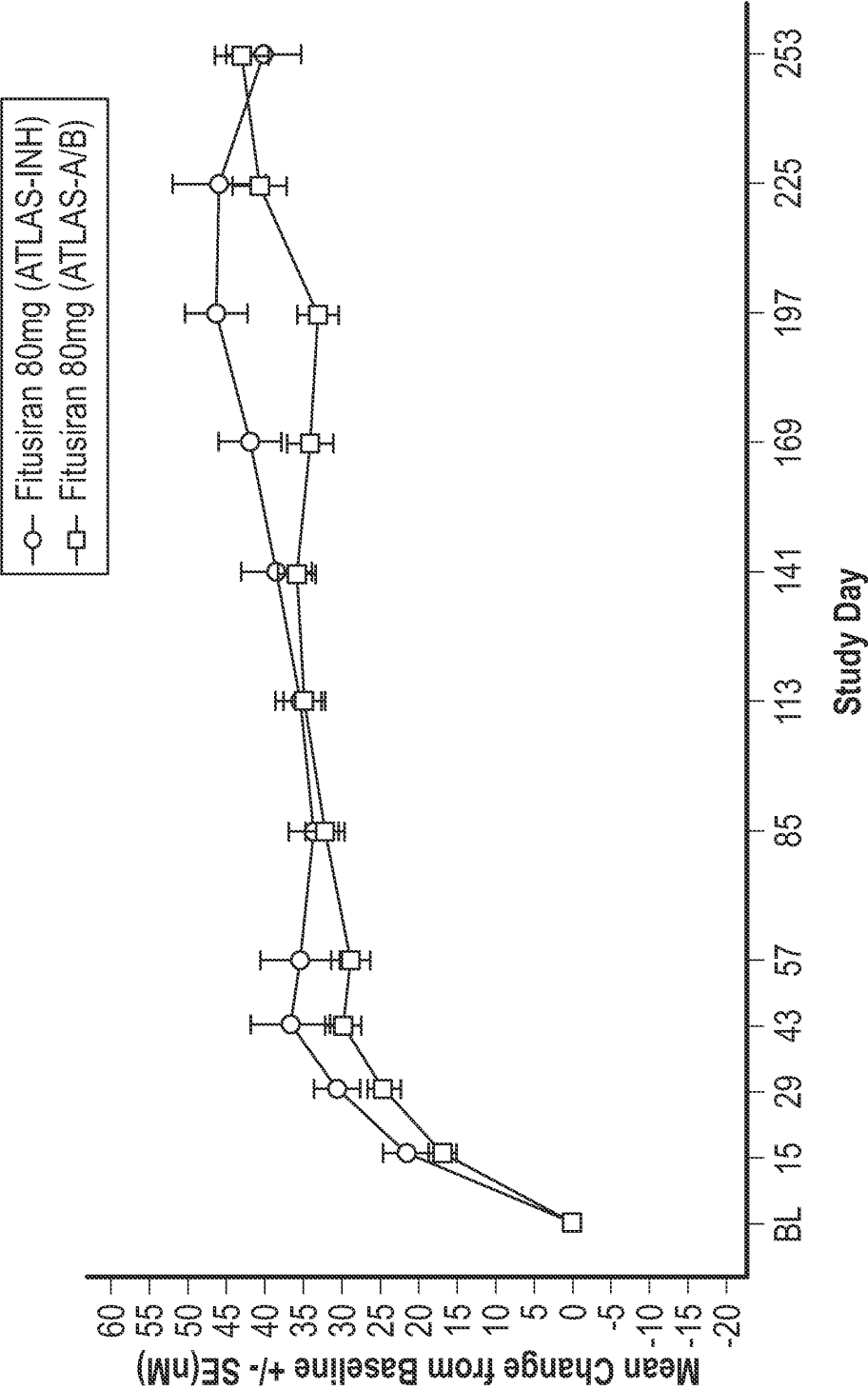


FIG. 11

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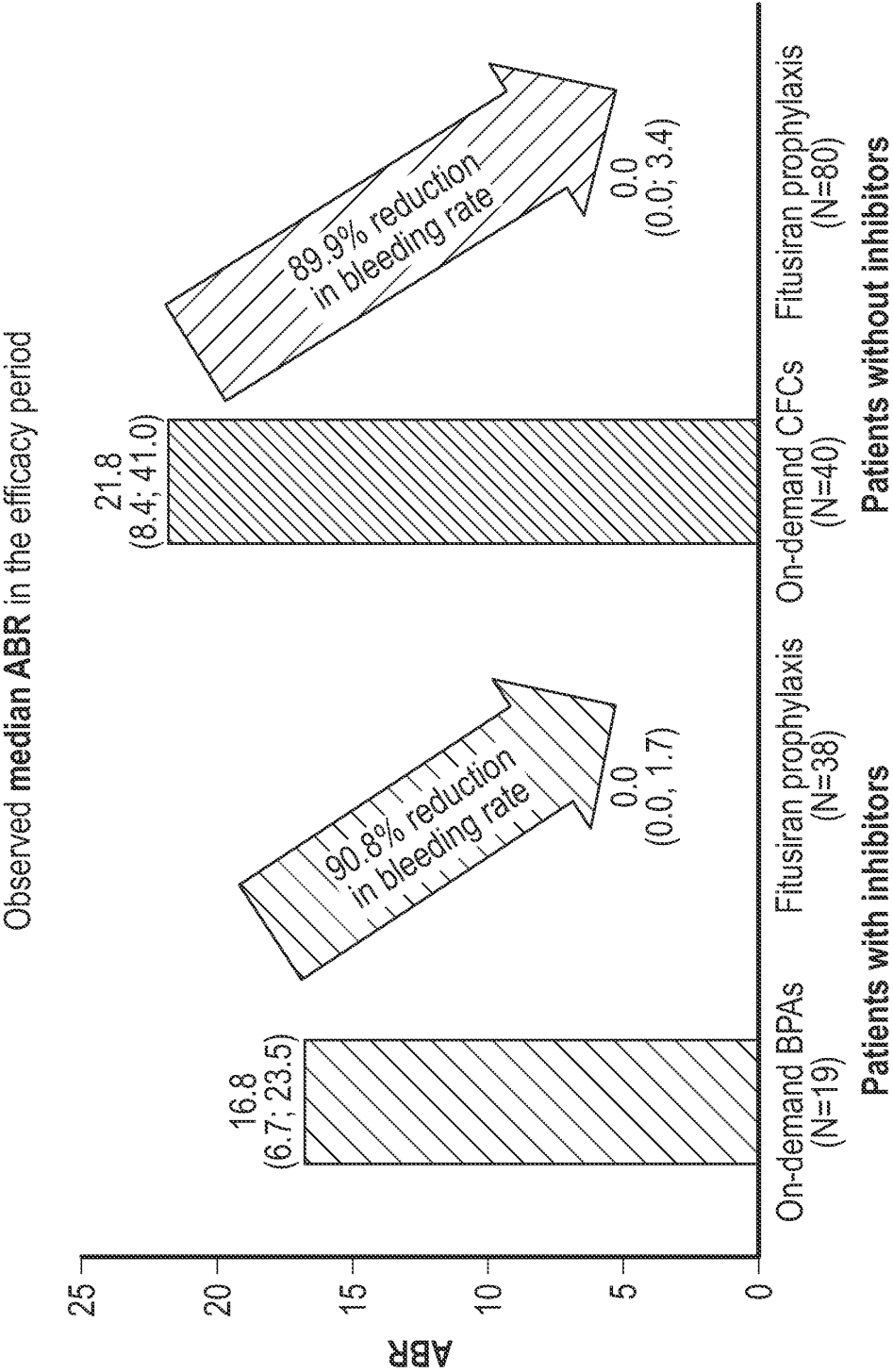


FIG. 12

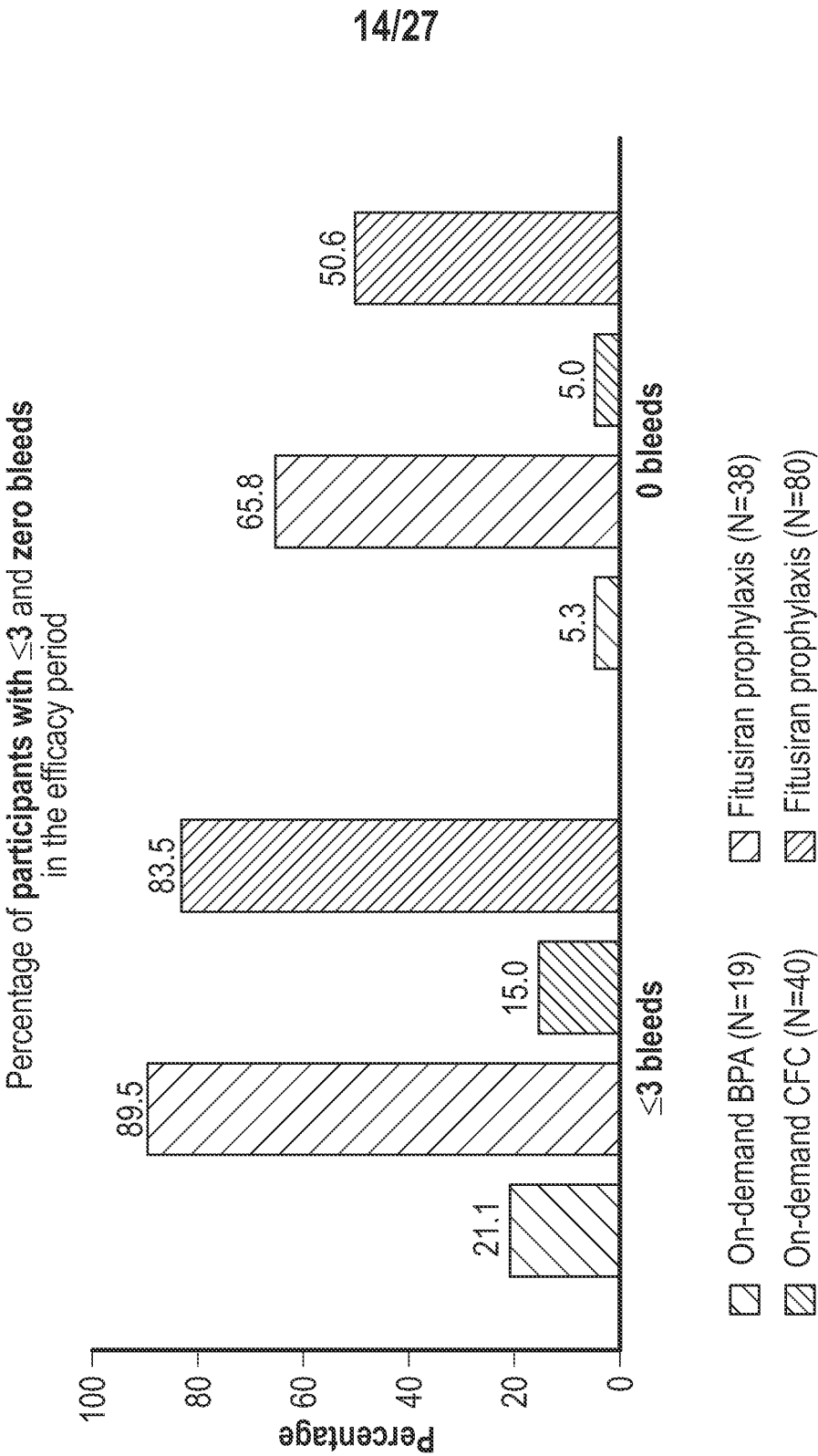


FIG. 13

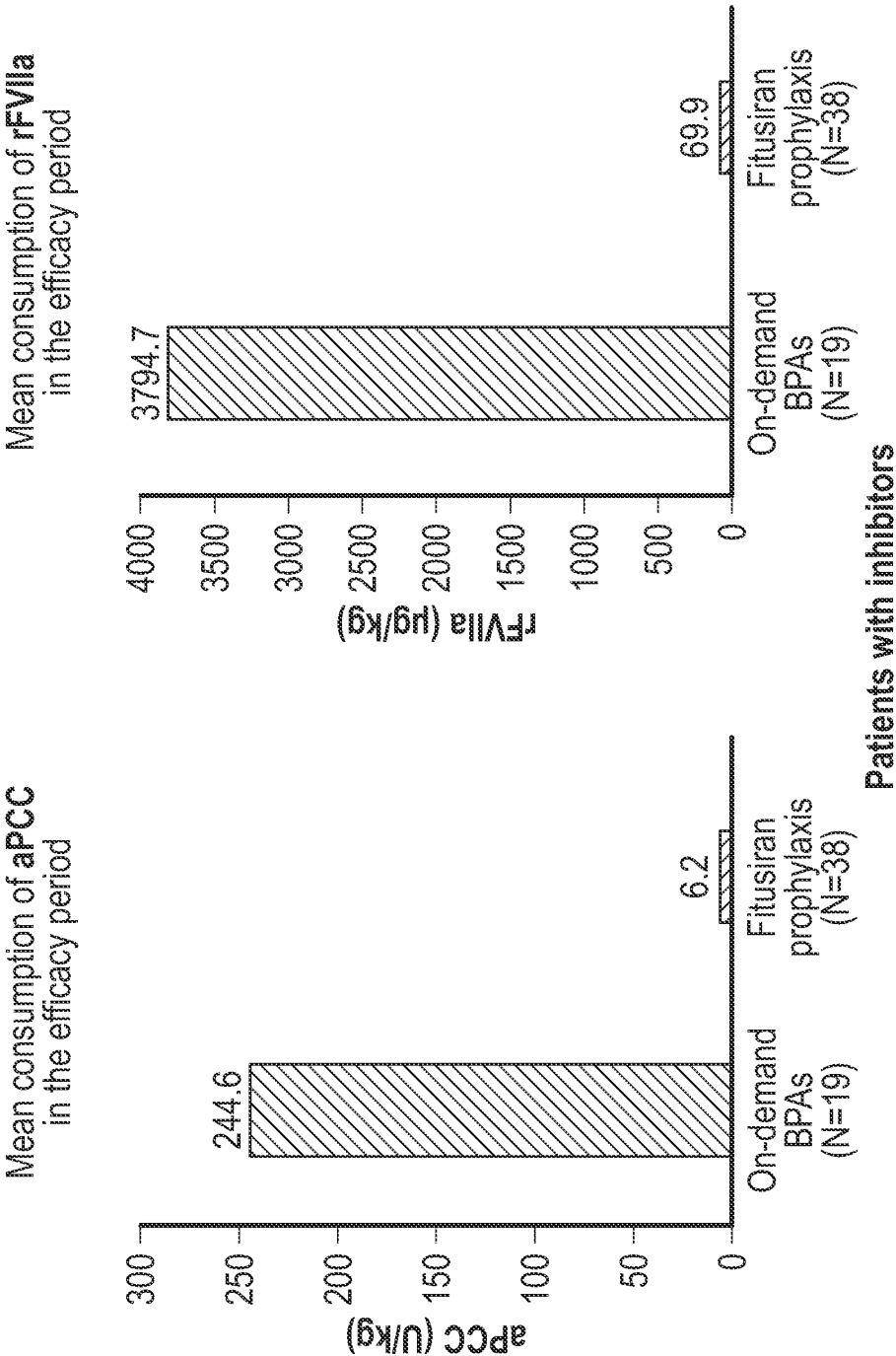
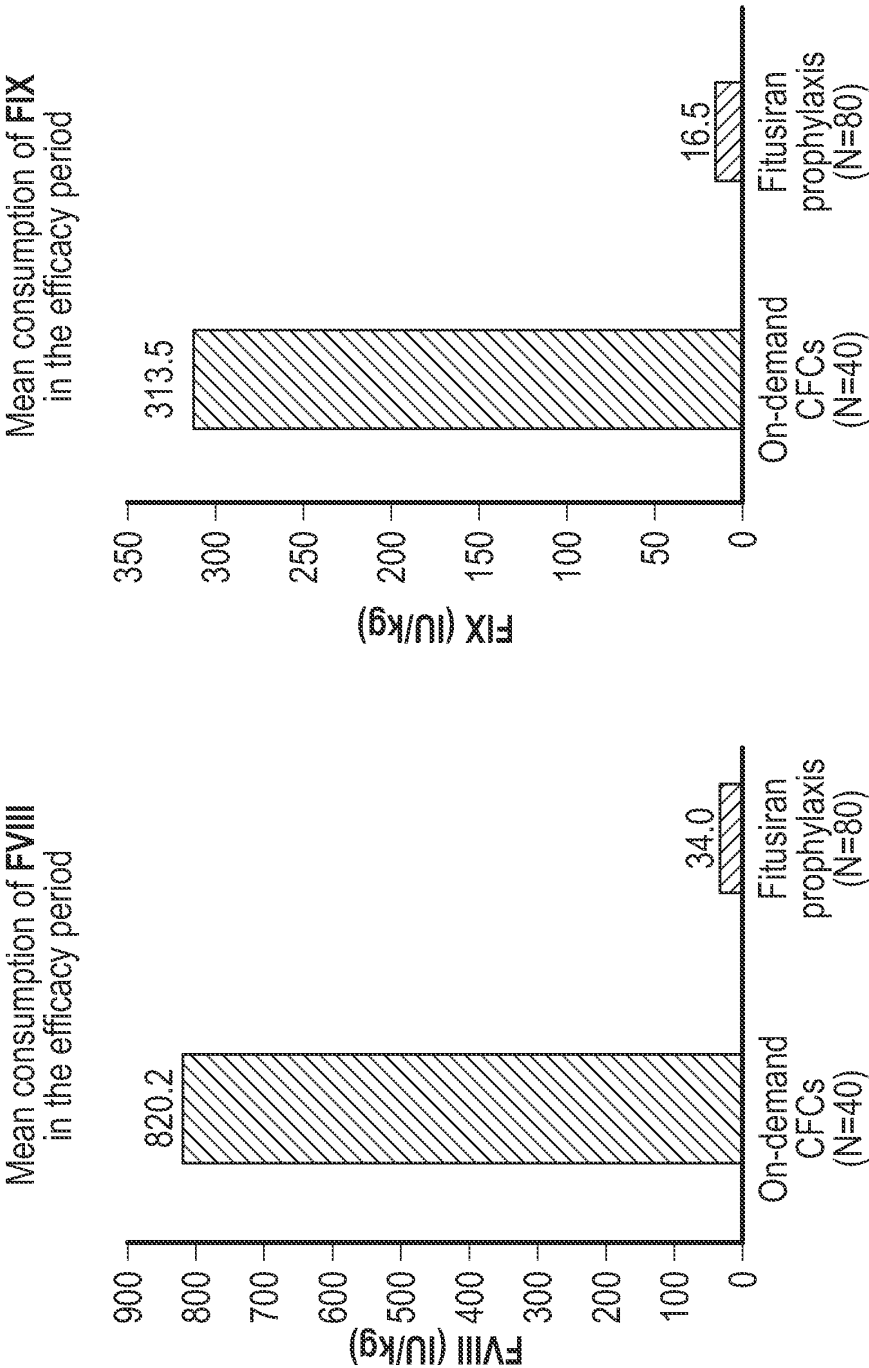


FIG. 14



Patients without inhibitors

FIG. 14 (Continued)

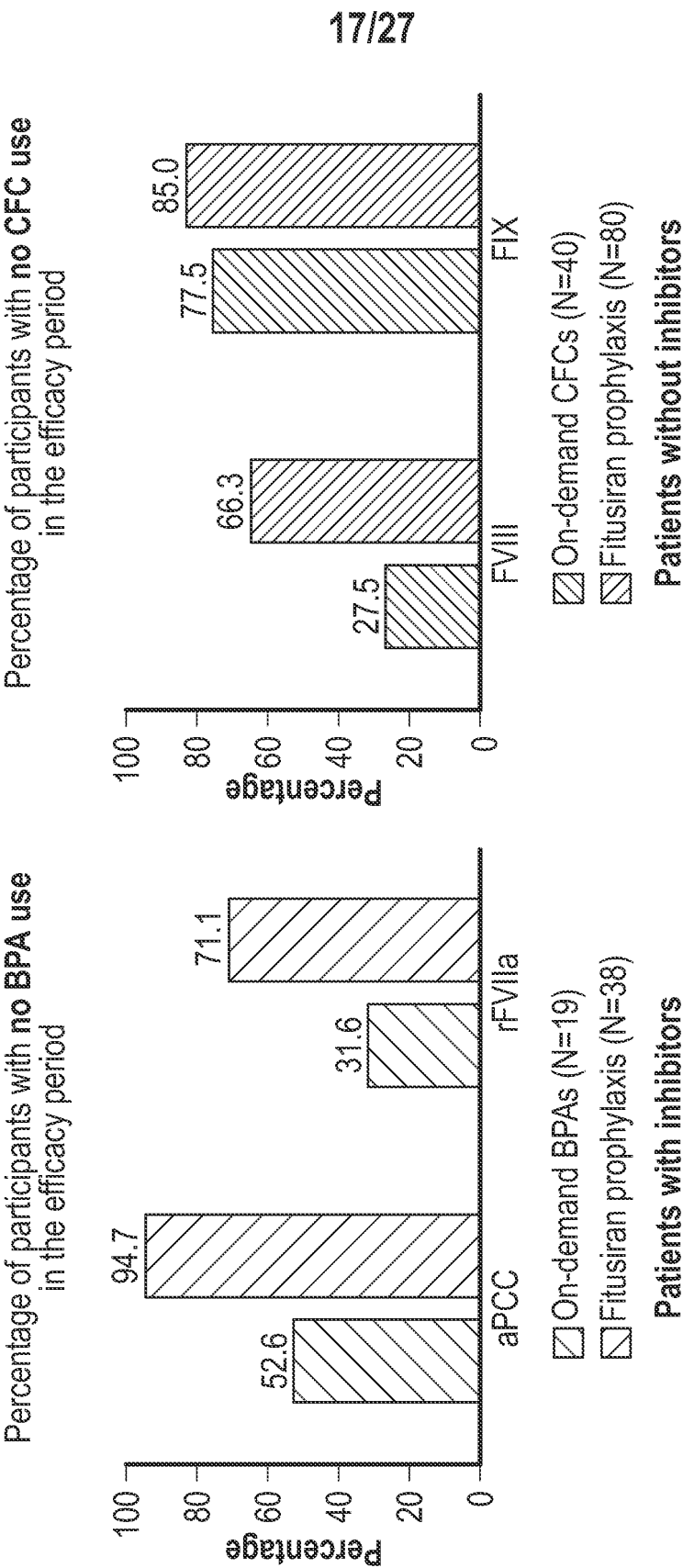


FIG. 15

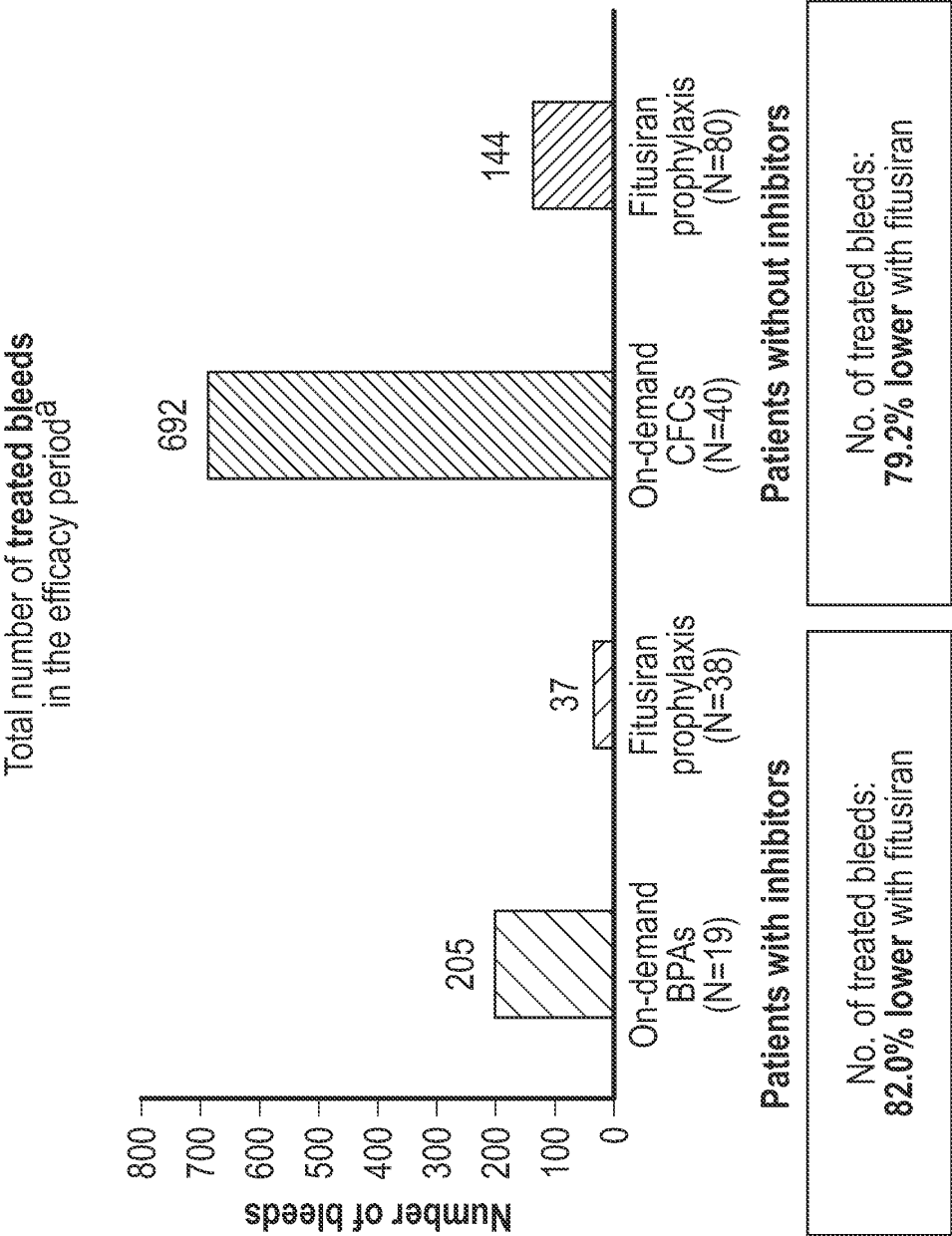


FIG. 16

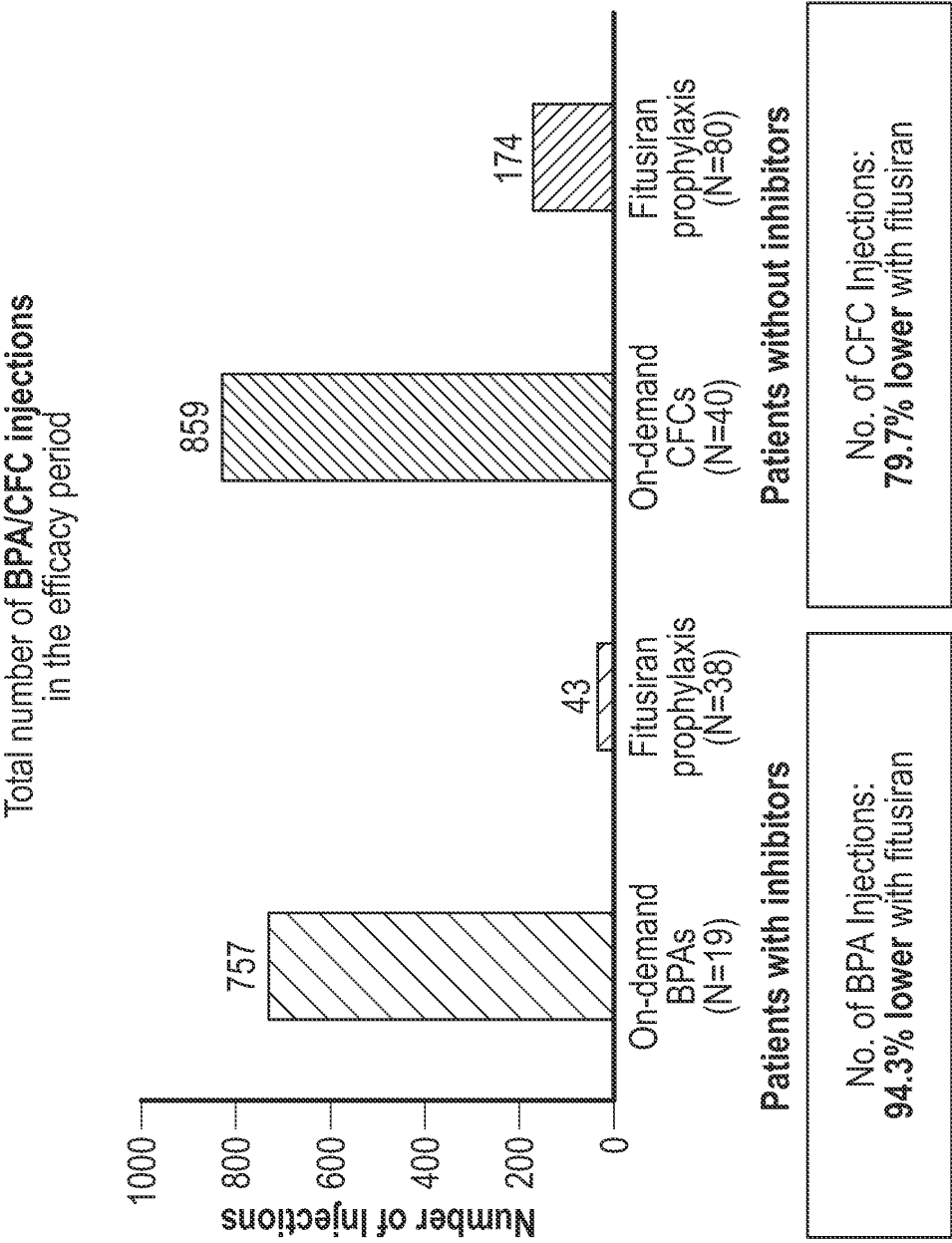


FIG. 16 (Continued)

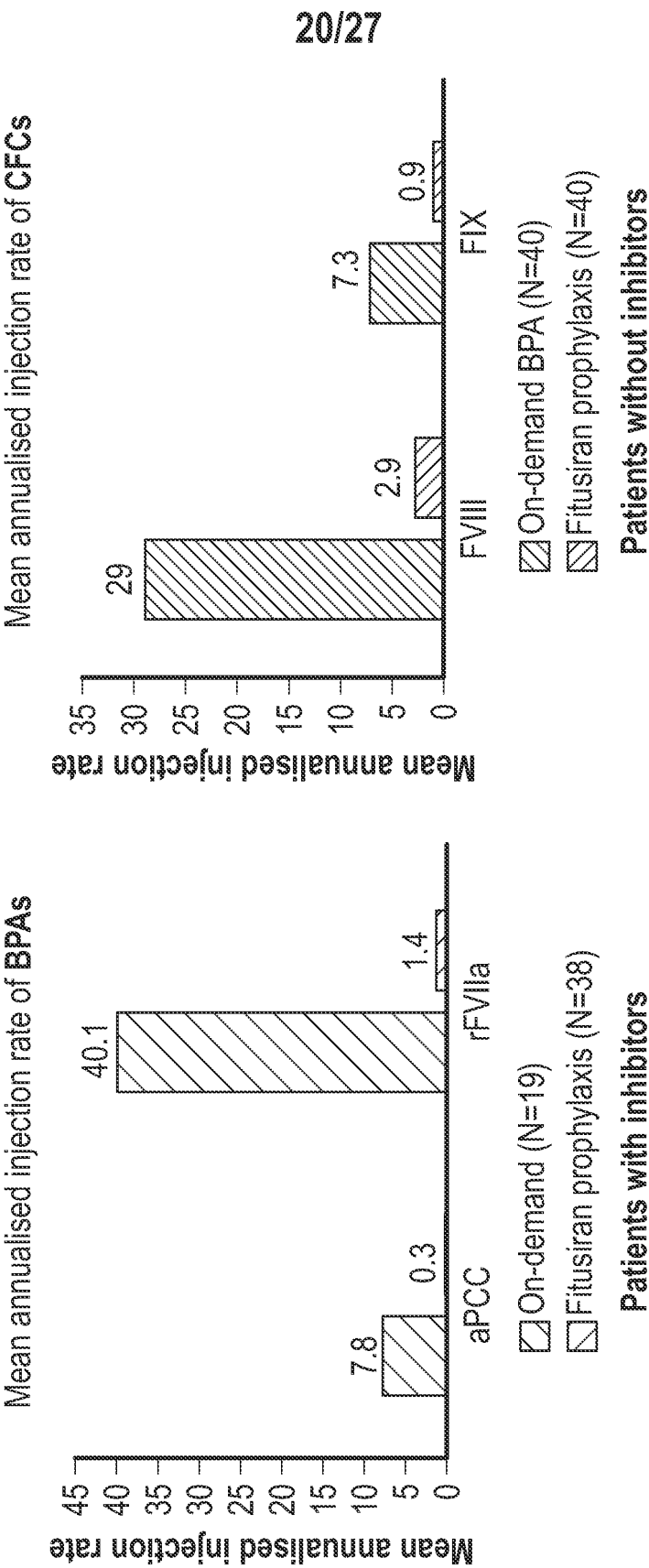


FIG. 17

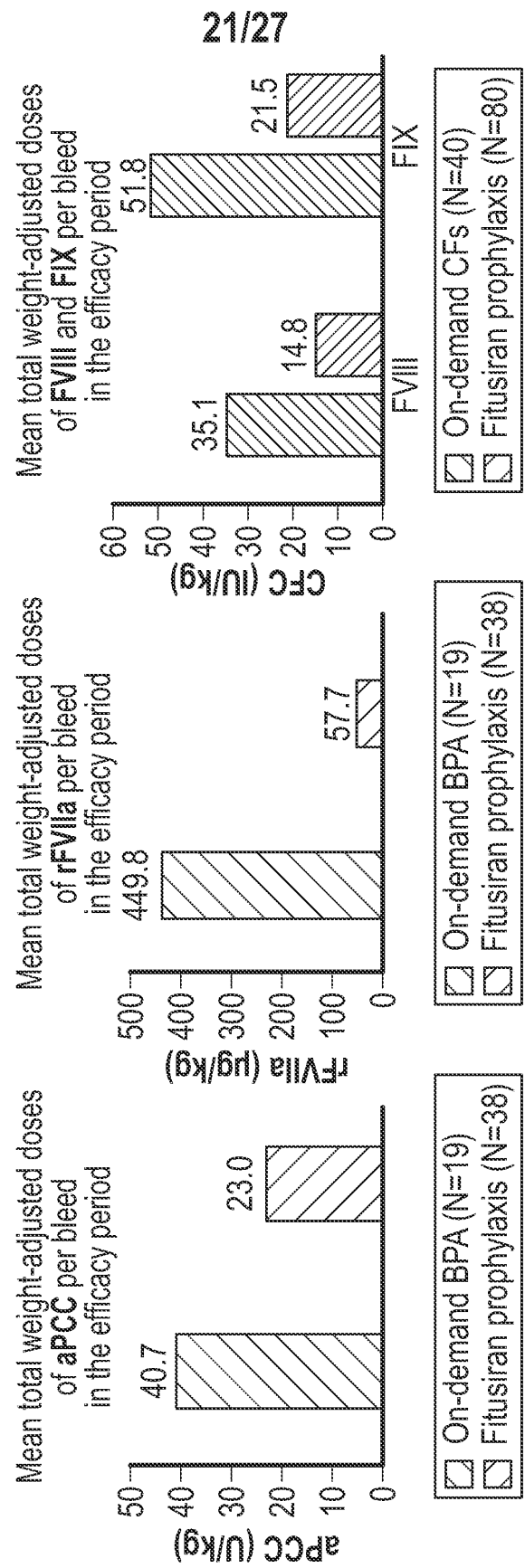


FIG. 18

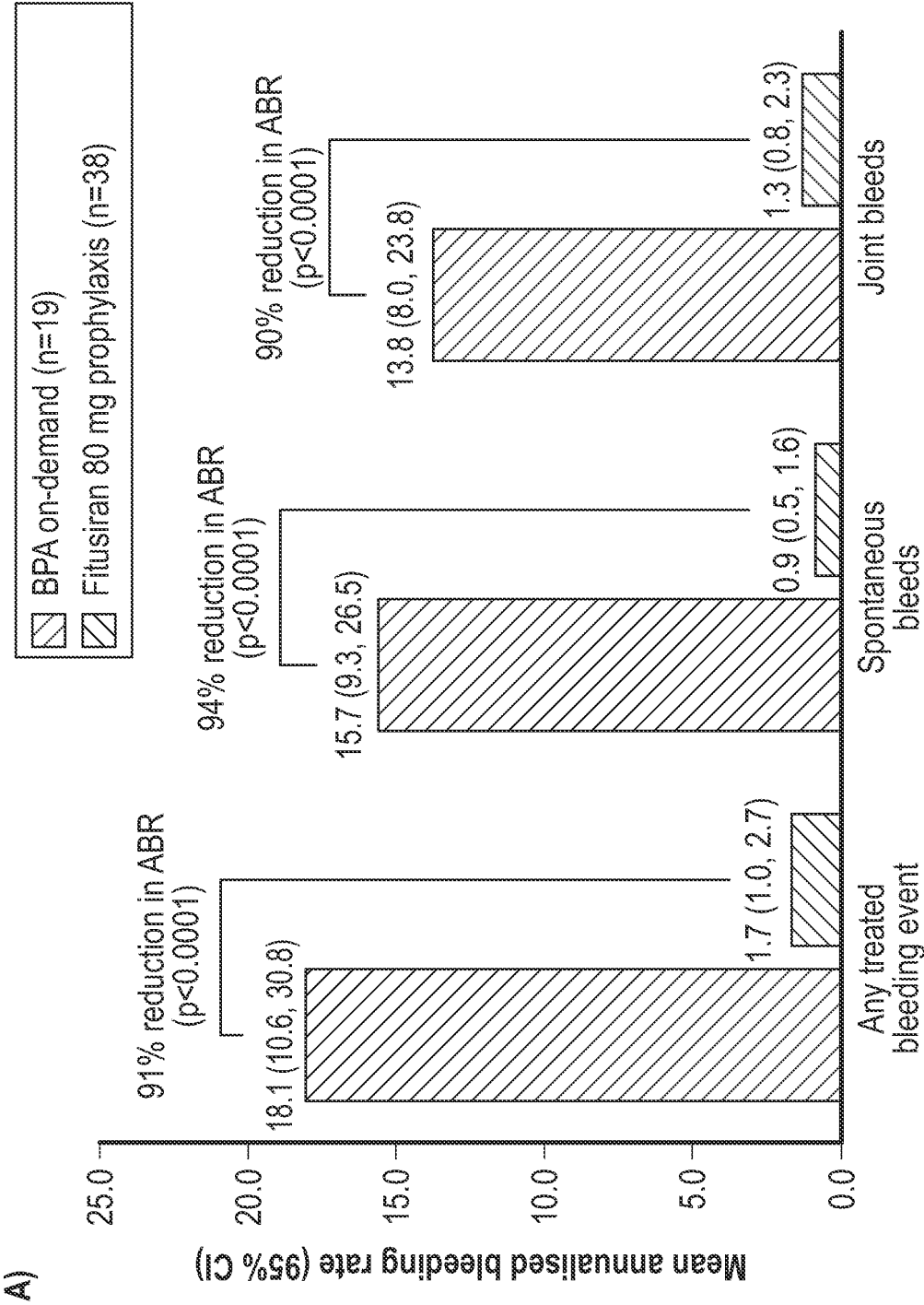


FIG. 19

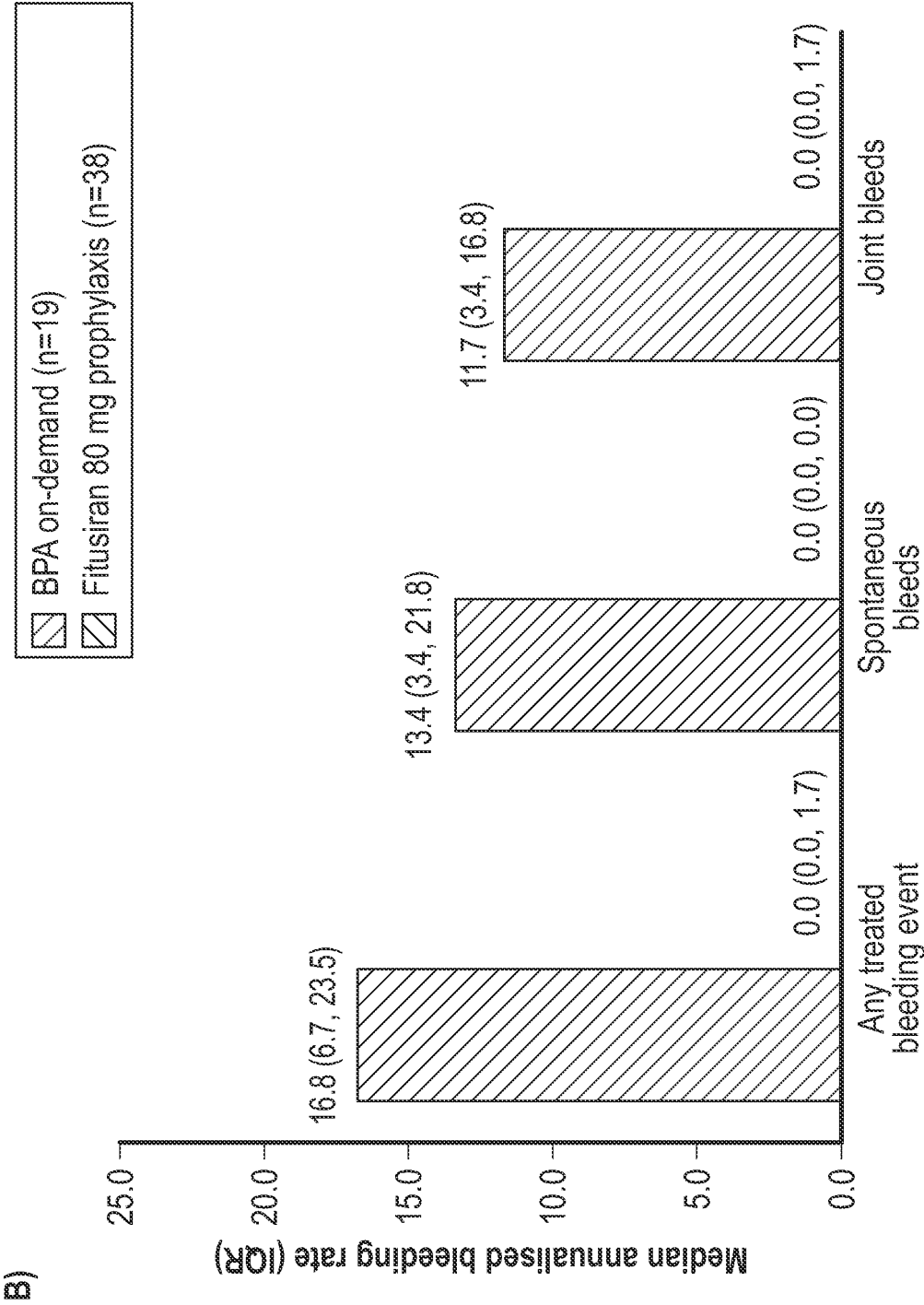


FIG. 19 (Continued)

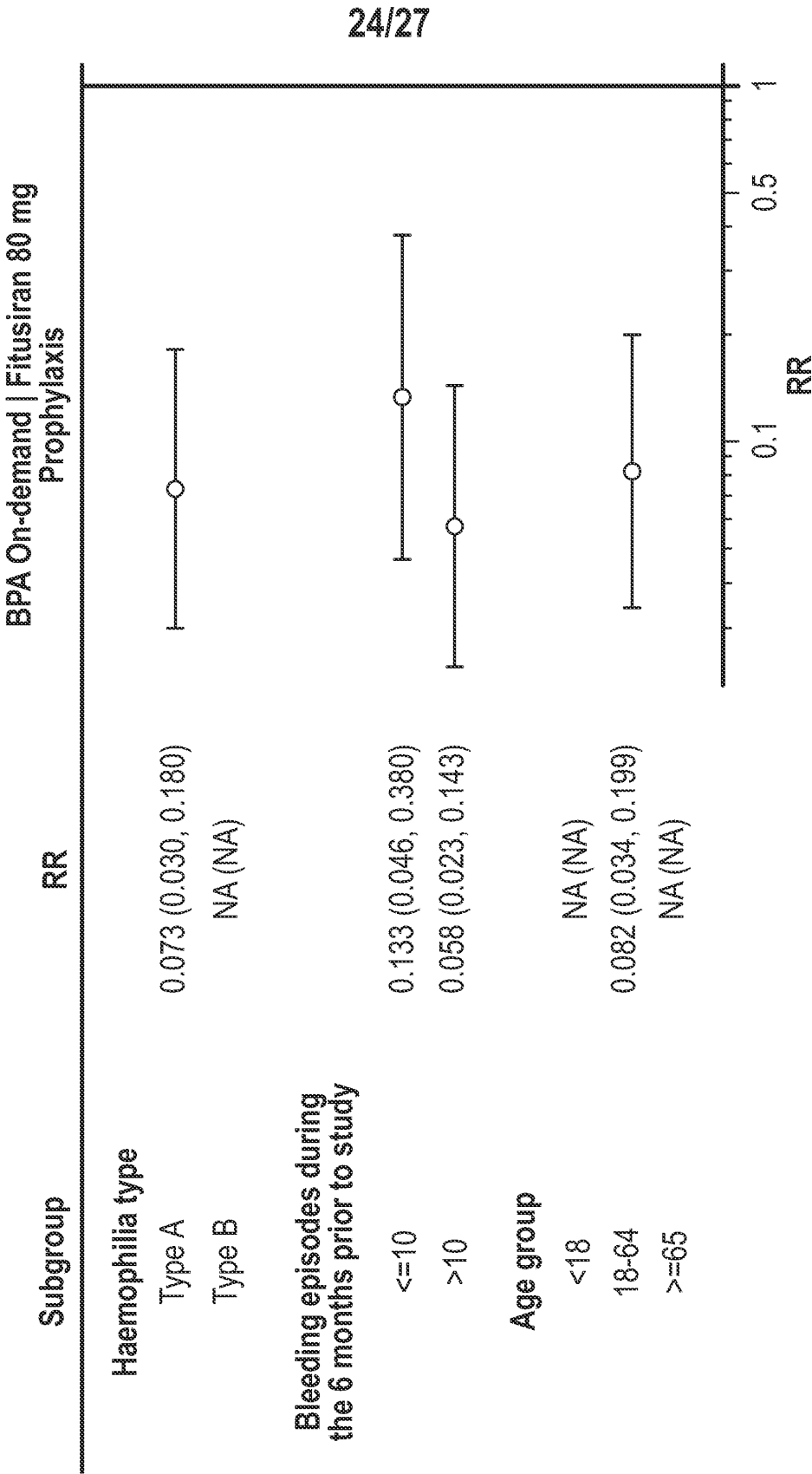


FIG. 20

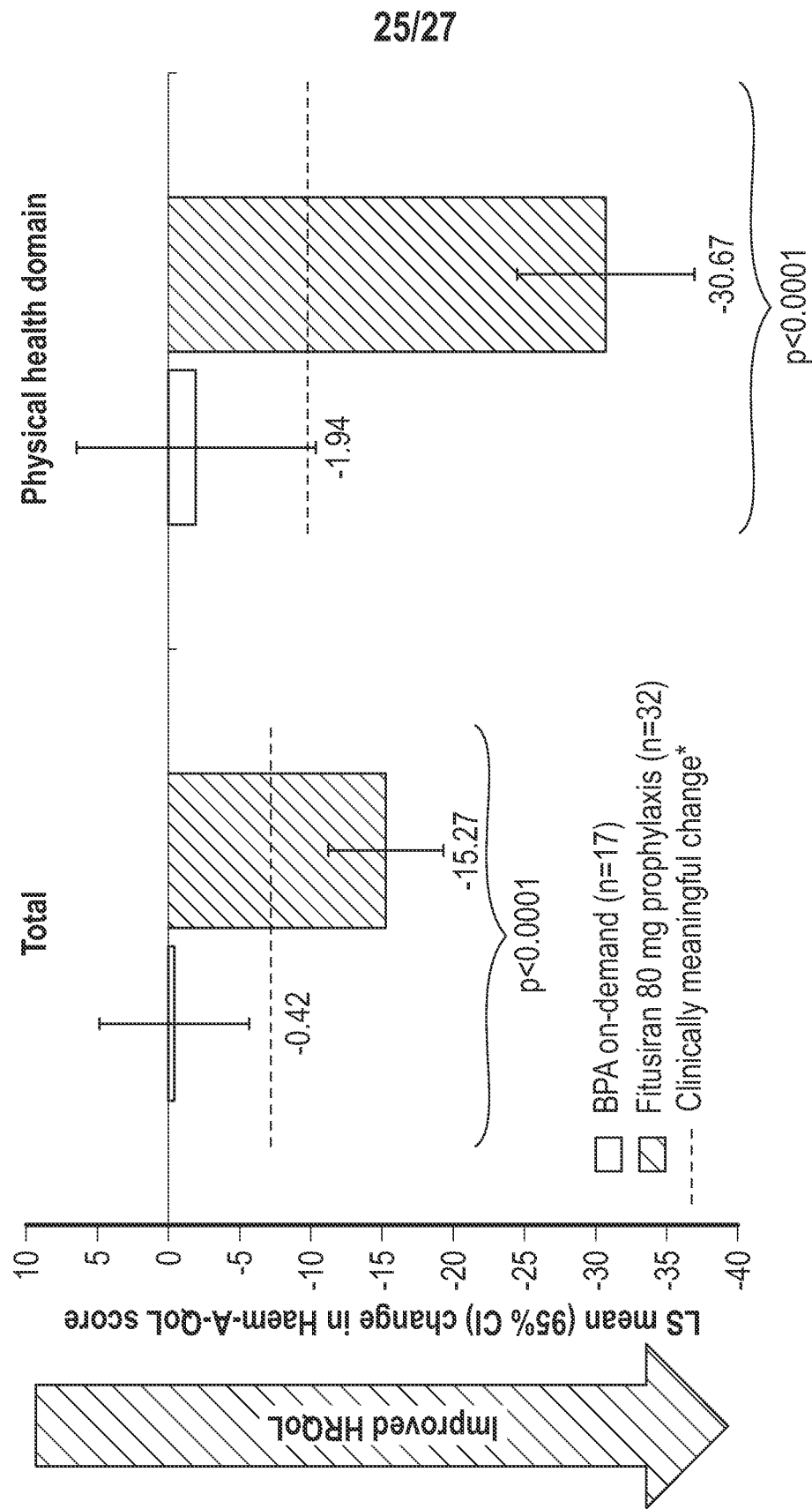


FIG. 21

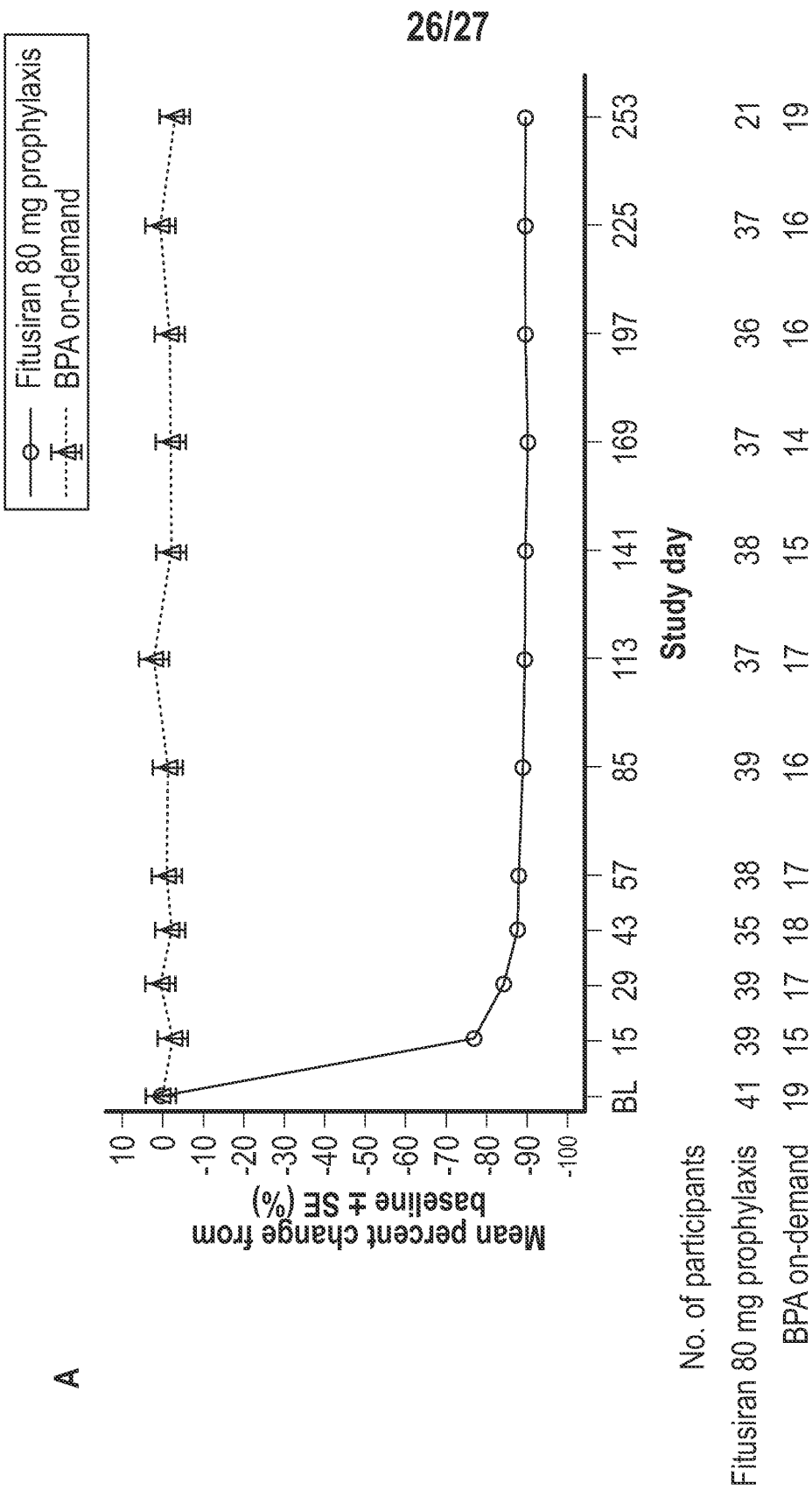


FIG. 22

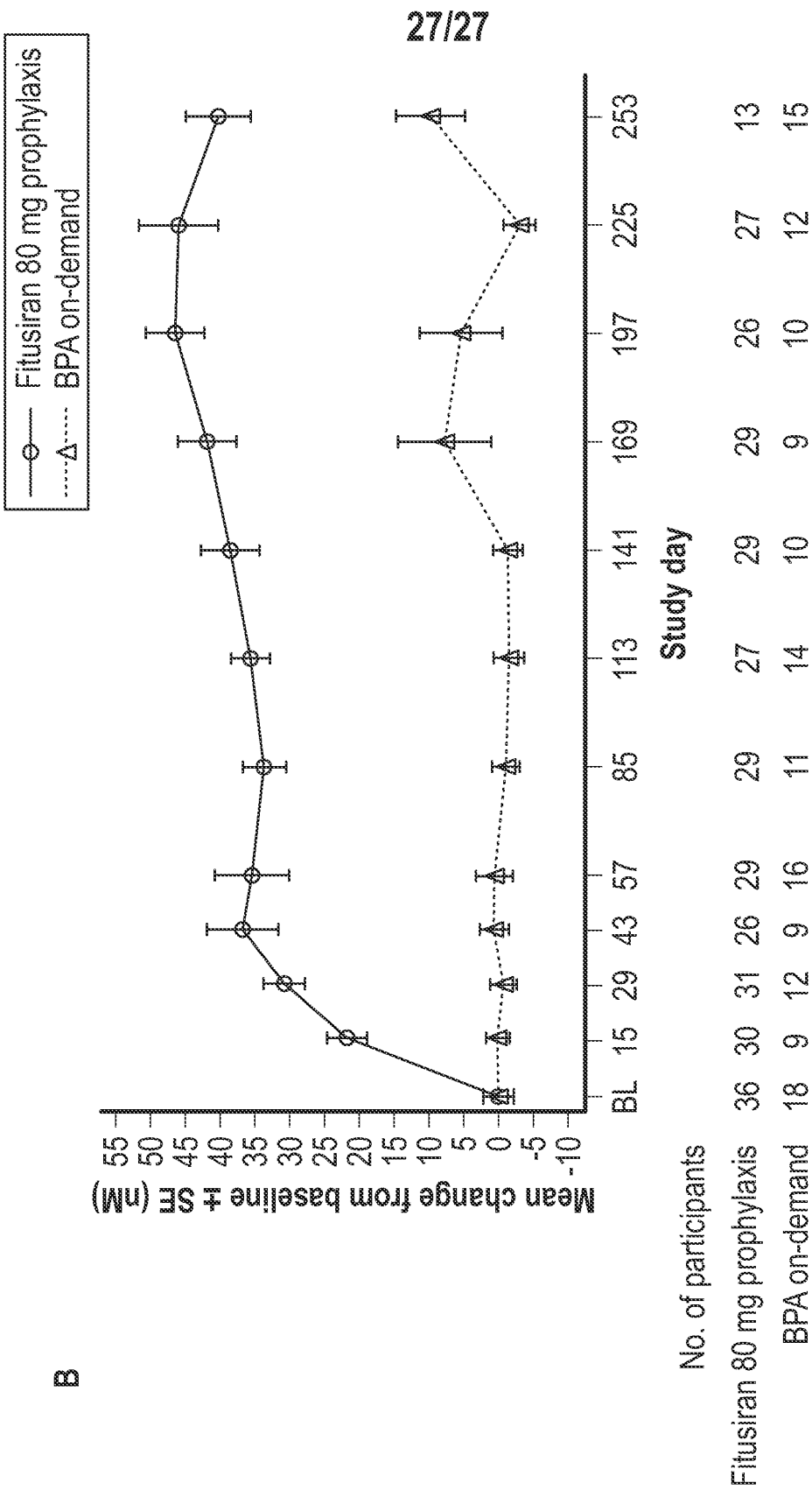


FIG. 22 (Continued)