Comparison of Fatal or Irreversible Events With Extended Duration Betrixaban Versus Standard Dose Enoxaparin in Acutely Ill Medical Patients: An APEX Trial Substudy

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

Citation
Gibson, C. M., S. Korjian, G. Chi, Y. Daaboul, P. Jain, D. Arbetter, S. Z. Goldhaber, et al. 2017. “Comparison of Fatal or Irreversible Events With Extended Duration Betrixaban Versus Standard Dose Enoxaparin in Acutely Ill Medical Patients: An APEX Trial Substudy.” Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease 6 (7): e006015. doi:10.1161/JAHA.117.006015. http://dx.doi.org/10.1161/JAHA.117.006015.

Published Version
doi:10.1161/JAHA.117.006015

Citable link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:34491882

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA
Comparison of Fatal or Irreversible Events With Extended-Duration Betrixaban Versus Standard Dose Enoxaparin in Acutely Ill Medical Patients: An APEX Trial Substudy

C. Michael Gibson, MS, MD; Serge Korjian, MD; Gerald Chi, MD; Yazan Daaboul, MD; Purva Jain, MPH; Douglas Arbetter, MPH; Samuel Z. Goldhaber, MD; Russel Hull, MBBS; Adrian F. Hernandez, MD; Renato D. Lopes, MD, MHS, PhD; Alex Gold, MD; Alexander T. Cohen, MD; Robert A. Harrington, MD; on behalf of the APEX Investigators*

Background—Extended-duration betrixaban showed a significant reduction in venous thromboembolism in the APEX trial (Acute Medically Ill VTE Prevention With Extended Duration Betrixaban Study). Given the variable clinical impact of different efficacy and safety events, one approach to assess net clinical outcomes is to include only those events that are either fatal or cause irreversible harm.

Methods and Results—This was a post hoc analysis of the APEX trial—a multicenter, double-blind, randomized controlled trial comparing extended-duration betrixaban versus standard-of-care enoxaparin. A composite of all fatal or irreversible safety (fatal bleeding or intracranial hemorrhage) and efficacy events (cardiopulmonary death, myocardial infarction, pulmonary embolism, and ischemic stroke) was evaluated in a time-to-first event analysis. In patients with positive D-dimer results, betrixaban reduced fatal or irreversible events at 35 to 42 days (4.80% versus 3.54%; hazard ratio, 0.73; absolute risk reduction, 1.26%; number needed to treat, 79 [P=0.033]) and at study end at 77 days (6.27% versus 4.36%; hazard ratio, 0.70; absolute risk reduction, 1.91%; number needed to treat, 52 [P=0.005]) versus enoxaparin. In all patients, betrixaban reduced fatal or irreversible events at 35 to 42 days (4.08% versus 2.90%; hazard ratio, 0.71; absolute risk reduction, 1.18%; number needed to treat, 86 [P=0.006]) and 77 days (5.17% versus 3.64%; hazard ratio, 0.70; absolute risk reduction, 1.53%; number needed to treat, 65 [P=0.002]).

Conclusions—Among hospitalized medically ill patients, extended-duration betrixaban demonstrated an ≈30% reduction in fatal or irreversible ischemic or bleeding events compared with standard-duration enoxaparin. A total of 65 patients would require treatment with betrixaban to prevent 1 fatal or irreversible event versus enoxaparin.

Clinical Trial Registration—URL: http://www.ClinicalTrials.gov. Unique identifier: NCT01583218. (J Am Heart Assoc. 2017;6: e006015. DOI: 10.1161/JAHA.117.006015.)

Key Words: death • intracranial hemorrhage • ischemic stroke • myocardial infarction • pulmonary embolism • venous thromboembolism

Therapeutic interventions are associated with both efficacy benefits and safety hazards. The net clinical outcome of an intervention can be assessed by combining measures of efficacy and safety. Some events may be transient and reversible and result in no permanent harm, which makes them challenging to weigh against each other. One way to ensure that the clinical impact of the efficacy and safety events that are being compared is similar is to include...
Betrixaban Reduces Fatal or Irreversible Events

Gibson et al

DOI: 10.1161/JAHA.117.006015

Clinical Perspective

What Is New?

• Among hospitalized medically ill patients through 77 days of follow-up, 1 fatal or irreversible event could be prevented by treating 65 patients with extended-duration betrixaban compared with standard-of-care enoxaparin.

What Are the Clinical Implications?

• Extended-duration thromboprophylaxis using an experimental oral factor Xa inhibitor may reduce the risk of fatal or irreversible events among hospitalized medically ill patients.

End Points

All safety and efficacy end points were adjudicated by members of a clinical events committee blinded to study group assignment. In this post hoc analysis, the primary end point was the composite of all fatal or irreversible ischemic and bleeding events. This composite end point was previously used in the clinical trial assessment of prasugrel. An irreversible efficacy end point was defined as death from ischemic cerebral or cardiopulmonary causes, including ischemic stroke, fatal arrhythmias, heart failure, venous thromboembolism, and sudden death from unknown causes, as well as nonfatal events that resulted in necrosis of tissue including nonfatal myocardial infarction (MI), nonfatal pulmonary embolism (PE), and nonfatal ischemic stroke. An irreversible safety end point was defined as fatal bleeding or intracranial hemorrhage. Nonfatal PE was not included as an outcome in sensitivity analysis because some patients with PE do not have necrosis of lung tissue.

Statistical Analysis

In the analysis of the 80- and 40-mg dose cohorts, the actual dose the patient was treated with was used.

All statistical analyses were programmed independently by two statisticians using SAS version 9.4 (SAS Institute Inc). Characteristics of the study population were evaluated using descriptive statistics. Data were expressed as frequencies and percentages for categorical variables, with denominators including all patients with available data. A time-to-first event survival analysis with right censorship was performed using a Cox proportional hazards regression model, where event rates were expressed as Kaplan–Meier estimates, and P values

Methods

Study Design and Population

APEX was a randomized, double-blind, double-dummy, active-controlled, multinational phase 3 clinical trial. The trial design and main results have been previously published. In brief, acutely medically ill men and women, 40 years or older, with reduced mobility and increased risk for venous thromboembolism hospitalized for either acute heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke were eligible for enrollment. Major exclusion criteria were active bleeding or a high risk of bleeding, severe renal insufficiency with creatinine clearance <15 mL/min, or any condition requiring prolonged anticoagulation or antiplatelet therapy.

Patients were randomly assigned in a 1:1 ratio to receive either standard-duration subcutaneous enoxaparin 40 mg once daily for 10±4 days plus oral betrixaban placebo once daily for 35 to 42 days or subcutaneous enoxaparin placebo once daily for 10±4 days plus active extended-duration oral betrixaban (loading dose of 160 mg for the first dose followed by 80 mg once daily for 35–42 days). The dose of study drug was adjusted to 40 mg among patients with renal insufficiency with creatinine clearance <30 mL/min (both enoxaparin and betrixaban doses were halved) and patients receiving concomitant strong P-glycoprotein inhibitors (only betrixaban dose was halved). Clinical outcomes were assessed between day 35 and day 42 and again at an additional 30±5 days after day 42. The modified intent-to-treat cohort was used, which included all randomized patients who had at least one dose of study drug. The primary and first cohort tested (cohort 1) included patients who had positive D-dimer results (≥2 times the upper limit of normal) by local laboratory assessment. Cohort 2 included patients who had positive D-dimer results or were 75 years and older. In addition, end points were assessed in all randomized patients (Figures S1 and S2). The study was approved by the local institutional review committees, and all enrolled participants provided informed consent.

Characteristics of the study population were evaluated using two statisticians using SAS version 9.4. All statistical analyses were programmed independently by

Characteristics of the study population were evaluated using two statisticians using SAS version 9.4. All statistical analyses were programmed independently by two statisticians using SAS version 9.4 (SAS Institute Inc). Characteristics of the study population were evaluated using descriptive statistics. Data were expressed as frequencies and percentages for categorical variables, with denominators including all patients with available data. A time-to-first event survival analysis with right censorship was performed using a Cox proportional hazards regression model, where event rates were expressed as Kaplan–Meier estimates, and P values

What Are the Clinical Implications?

• Extended-duration thromboprophylaxis using an experimental oral factor Xa inhibitor may reduce the risk of fatal or irreversible events among hospitalized medically ill patients.

Clinical Perspective

What Is New?

• Among hospitalized medically ill patients through 77 days of follow-up, 1 fatal or irreversible event could be prevented by treating 65 patients with extended-duration betrixaban compared with standard-of-care enoxaparin.

What Are the Clinical Implications?

• Extended-duration thromboprophylaxis using an experimental oral factor Xa inhibitor may reduce the risk of fatal or irreversible events among hospitalized medically ill patients.

End Points

All safety and efficacy end points were adjudicated by members of a clinical events committee blinded to study group assignment. In this post hoc analysis, the primary end point was the composite of all fatal or irreversible ischemic and bleeding events. This composite end point was previously used in the clinical trial assessment of prasugrel. An irreversible efficacy end point was defined as death from ischemic cerebral or cardiopulmonary causes, including ischemic stroke, fatal arrhythmias, heart failure, venous thromboembolism, and sudden death from unknown causes, as well as nonfatal events that resulted in necrosis of tissue including nonfatal myocardial infarction (MI), nonfatal pulmonary embolism (PE), and nonfatal ischemic stroke. An irreversible safety end point was defined as fatal bleeding or intracranial hemorrhage. Nonfatal PE was not included as an outcome in sensitivity analysis because some patients with PE do not have necrosis of lung tissue.
were reported using the log-rank test. Events were analyzed through visit 3 or day 42 to reflect the primary analysis and through end of study at day 77 as an exploratory assessment. All events (efficacy or safety) were considered to have equal statistical weight. A $P<0.05$ was considered statistically significant.

### Results

The baseline characteristics of the two cohorts were well matched. The median time overall on enoxaparin/enoxaparin placebo and betrixaban/betrixaban placebo was 9 (interquartile range, 7–13) and 36 (interquartile range, 34–39) days, respectively.

#### Table 1. Composite of Fatal and Irreversible Events

| Outcome*                                                                 | Through Visit 3 or Day 42 | Through Day 77 |
|-------------------------------------------------------------------------|---------------------------|----------------|
|                                                                          | Enoxaparin†               | Enoxaparin†    |
|                                                                          | Betrixaban                | 101/2314 (4.4) | 101/2314 (4.4) |
|                                                                          | Enoxaparin†               | 145/2313 (6.3) |
| Cohort 1                                                                 |                           |                |
| Composite, No./total No. (%)                                            | 82/2314 (3.5)             | 111/2313 (4.8) |
|                                                                          | 101/2314 (4.4)             | 145/2313 (6.3) |
| Ischemic events, No.                                                     |                           |                |
| Ischemic cardiopulmonary death†                                         | 68                        | 74             |
|                                                                          | 84                        | 99             |
| Nonfatal ischemic stroke                                                | 5                         | 11             |
|                                                                          | 7                         | 14             |
| MI                                                                      | 11                        | 12             |
|                                                                          | 12                        | 18             |
| Nonfatal pulmonary embolism                                             | 5                         | 17             |
|                                                                          | 5                         | 20             |
| Bleed events, No.                                                       |                           |                |
| Fatal bleed                                                             | 0                         | 1              |
|                                                                          | 0                         | 1              |
| Intracranial hemorrhage                                                 | 0                         | 3              |
|                                                                          | 0                         | 4              |
| Cohort 2                                                                 |                           |                |
| Composite, No./total No. (%)                                            | 105/3407 (3.1)            | 139/3391 (4.1) |
|                                                                          | 133/3407 (3.9)            | 180/3391 (5.3) |
| Ischemic events, No.                                                     |                           |                |
| Ischemic cardiopulmonary death†                                         | 81                        | 92             |
|                                                                          | 103                       | 120            |
| Nonfatal ischemic stroke                                                | 8                         | 15             |
|                                                                          | 10                        | 20             |
| MI                                                                      | 14                        | 15             |
|                                                                          | 15                        | 22             |
| Nonfatal pulmonary embolism                                             | 9                         | 18             |
|                                                                          | 9                         | 22             |
| Bleed events, No.                                                       |                           |                |
| Fatal bleed                                                             | 1                         | 1              |
|                                                                          | 1                         | 1              |
| Intracranial hemorrhage                                                 | 1                         | 5              |
|                                                                          | 1                         | 6              |
| All randomized patients                                                 |                           |                |
| Composite, No./total No. (%)                                            | 109/3759 (2.9)            | 153/3754 (4.1) |
|                                                                          | 137/3759 (3.6)            | 194/3754 (5.2) |
| Ischemic events, No.                                                     |                           |                |
| Ischemic cardiopulmonary death†                                         | 84                        | 103            |
|                                                                          | 106                       | 131            |
| Nonfatal ischemic stroke                                                | 8                         | 16             |
|                                                                          | 10                        | 21             |
| MI                                                                      | 14                        | 17             |
|                                                                          | 15                        | 24             |
| Nonfatal pulmonary embolism                                             | 10                        | 20             |
|                                                                          | 10                        | 24             |
| Bleed events, No.                                                       |                           |                |
| Fatal bleed                                                             | 1                         | 1              |
|                                                                          | 1                         | 1              |
| Intracranial hemorrhage                                                 | 1                         | 5              |
|                                                                          | 1                         | 6              |

*Data for safety outcomes were evaluated through visit 3 or day 42. The breakdown of events adds up to more than the composite events because the composite includes only the first event the patient experienced. Modified intention-to-treat population for cohort 1 and cohort 2 analyses.

†Enoxaparin was administered for 10±4 days, followed by oral betrixaban placebo for 35 to 42 days.

‡Includes fatal pulmonary embolism/venous thromboembolism—confirmed, fatal pulmonary embolism/venous thromboembolism—possible, fatal pulmonary embolism/venous thromboembolism—probable, arrhythmic event, heart failure, fatal ischemic stroke, fatal myocardial infarction (MI), and sudden death of unknown cause.

DOI: 10.1161/JAHA.117.006015
Composite event rates were consistently lower in the betrixaban arm across all cohorts, including and excluding nonfatal PE (Tables 1 and 2). In cohort 1 (patients with positive D-dimer results), there was a significant reduction in fatal or irreversible events at both visit 3 (35–42 days) and visit 4 (77 days) (Figure 1). Given the positive results observed in cohort 1, cohort 2 (patients with positive D-dimer results or age older than 75 years) was then evaluated, which showed a similar reduction in events at visit 3 (3.1% versus 4.1%; hazard ratio [HR], 0.75 [95% CI, 0.58–0.96]; \(P=0.02\)) and visit 4 (3.9% versus 5.3%; HR, 0.74 [95% CI, 0.59–0.92]; \(P=0.007\)) in favor of betrixaban over enoxaparin. Given the significant results in cohort 2, cohort 3 (all randomized patients) was therefore tested and also demonstrated a significant reduction in fatal or irreversible events (Figure 2) in favor of betrixaban over enoxaparin. The number needed to treat to prevent 1 efficacy event was 65 when comparing betrixaban versus enoxaparin in all randomized patients through the end of the study. Betrixaban did not show higher risk for safety events from the composite when compared with enoxaparin, thus the number needed to harm could not be calculated. In all analyses, the improvement in net clinical

**Table 2. Composite of Fatal and Irreversible Events Excluding Nonfatal Pulmonary Embolism**

| Outcome* | Through Visit 3 or Day 42 | Through Day 77 |
|----------|---------------------------|----------------|
|          | Betrixaban | Enoxaparin† | Betrixaban | Enoxaparin† |
| Cohort 1 |            |             |            |             |
| Composite, No./Total No. (%) | 78/2314 (3.4) | 96/2313 (4.2) | 97/2314 (4.2) | 130/2313 (5.6) |
| Ischemic events, No. | | | | |
| Ischemic cardiopulmonary death‡ | 68 | 72 | 84 | 99 |
| Nonfatal ischemic stroke | 5 | 11 | 7 | 14 |
| Nonfatal MI | 11 | 12 | 12 | 18 |
| Bleed events, No. | | | | |
| Fatal bleed | 0 | 1 | 0 | 1 |
| Intracranial hemorrhage | 0 | 3 | 0 | 4 |
| Cohort 2 | | | | |
| Composite, No./Total No. (%) | 98/3407 (2.9) | 124/3391 (3.7) | 126/3340 (3.7) | 164/3391 (4.8) |
| Ischemic events, No. | | | | |
| Ischemic cardiopulmonary death | 81 | 90 | 103 | 120 |
| Nonfatal ischemic stroke | 8 | 15 | 10 | 20 |
| Nonfatal MI | 14 | 15 | 15 | 22 |
| Bleed events, No. | | | | |
| Fatal bleed | 1 | 1 | 1 | 1 |
| Intracranial hemorrhage | 1 | 5 | 1 | 6 |
| All randomized patients | | | | |
| Composite, No./Total No. (%) | 101/3759 (2.7) | 136/3754 (3.6) | 129/3759 (3.4) | 176/3754 (4.7) |
| Ischemic events, No. | | | | |
| Ischemic cardiopulmonary death | 84 | 101 | 106 | 131 |
| Nonfatal ischemic stroke | 8 | 16 | 10 | 21 |
| Nonfatal MI | 14 | 17 | 15 | 24 |
| Bleed events, No. | | | | |
| Fatal bleed | 1 | 1 | 1 | 1 |
| Intracranial hemorrhage | 1 | 5 | 1 | 6 |

*Data for safety outcomes were evaluated through visit 3 or day 42 and day 77. The breakdown of events adds up to more than the composite events because the composite includes only the first event the patient experienced. Modified intention-to-treat population for cohort 1 and cohort 2 analyses.

†Enoxaparin was administered for 10±4 days, followed by oral betrixaban placebo for 35 to 42 days.

‡Includes fatal pulmonary embolism/venous thromboembolism—confirmed, fatal pulmonary embolism/venous thromboembolism—possible, fatal pulmonary embolism/venous thromboembolism—probable, arrhythmic event, heart failure, fatal ischemic stroke, fatal myocardial infarction (MI), and sudden death of unknown cause.
outcomes began to emerge during the parenteral period of therapy.

In a sensitivity analysis, which excluded nonfatal PE from the composite end point, betrixaban administration was associated with a similar reduction in the risk of the other fatal or irreversible events, which reached statistical significance at 77 days, end of study (Figures S3 and S4). In addition, in a sensitivity analysis excluding nonfatal

Figure 1. Time to first fatal or irreversible event in cohort 1. *End of trial defined as final follow-up visit (30+5 days after visit 3). Enoxaparin was administered for 10±4 days, followed by oral betrixaban placebo for 35 to 42 days. ARR indicates absolute risk reduction; HR, hazard ratio; NNT, number needed to treat.

Figure 2. Time to first fatal or irreversible event in the randomized population. *End of trial defined as final follow-up visit (30+5 days after visit 3). Enoxaparin was administered for 10±4 days, followed by oral betrixaban placebo for 35 to 42 days. ARR indicates absolute risk reduction; HR, hazard ratio; NNT, number needed to treat.

DOI: 10.1161/JAHA.117.006015
There was a reduction of fatal or irreversible events in all randomized patients comparing betrixaban versus enoxaparin through visit 3, or day 42 (HR, 0.71; 95% CI, 0.54–0.94 [P=0.016]) and through visit 4, or day 77 (HR, 0.72; 95% CI, 0.57–0.92 [P=0.008]). As a sensitivity analysis, the data were analyzed using the Cochran-Mantel-Haenszel test, which also yielded a significant event reduction across all cohorts of patients and time windows (Table S1). In addition, a sensitivity analysis that replaced cardiopulmonary death with all-cause mortality showed no significant benefit across all cohorts through visit 3 and the end of the study (Table S2).

In a series of similar analyses limited to patients receiving the full dose of betrixaban (80 mg), there was a consistent reduction in fatal or irreversible events as compared with enoxaparin (Table S3). Fatal or irreversible events were significantly reduced in both cohort 1 and all randomized patients (Figure 3 and Figure S5). In the smaller group of patients treated with the adjusted dose of betrixaban (40 mg), there was no significant reduction in events versus enoxaparin (Table S4 and Figure S6).

Of the 6 patients in the enoxaparin arm who experienced intracranial hemorrhages, 3 occurred while receiving enoxaparin and the remaining occurred while receiving either betrixaban placebo or no drug at all. No patients had renal insufficiency, and 5 of the 6 patients had creatinine clearances ≥60, while one had a clearance 30 to <60.

There was a significant reduction in the incidence of the traditional cardiovascular triple end point of cardiovascular death, MI, and all-cause stroke with extended-duration betrixaban versus standard duration enoxaparin in all randomized patients through visit 3 and visit 4. There was a 27% reduction in relative risk at visit 3 (2.29% versus 3.14%, P=0.023) and 25% at visit 4 (2.98% versus 3.97%, P=0.002) (Figure S7).

**Discussion**

Assessment of net clinical outcome, the combined impact of efficacy and safety data, is a commonly requested evaluation on the part of healthcare providers, payers, and regulators. The decision to administer an agent is a binary decision (either yes or no), and safety and efficacy in making such a decision must both be considered simultaneously. In many analyses, reversible bleeding events with no permanent sequelae are combined with intracranial hemorrhage and fatal bleeding, which cause irreversible harm. Some analyses rely on a time-to-first bleeding event methodology. In such analyses, if the first event is minor, it may obscure the clinical impact of a later event associated with fatal or irreversible harm. As a relevant precedent, the Food and Drug Administration approved prasugrel based on its reduction of fatal and irreversible events related to either ischemia end points for efficacy or bleeding for safety and

---

**Figure 3.** Time to first fatal or irreversible event in the randomized population—full dose (80 mg). *End of trial defined as final follow-up visit (30±5 days after visit 3). Enoxaparin was administered for 10±4 days, followed by oral betrixaban placebo for 35 to 42 days. ARR indicates absolute risk reduction; HR, hazard ratio; NNT, number needed to treat.
Betrixaban Reduces Fatal or Irreversible Events  
Gibson et al

published their method to focus on fatal and irreversible events. Based on this important precedent, we adopted a similar approach. The present study assessed outcomes during a relatively short period of ≈2 months. If similar risk reductions were maintained over a longer duration of follow-up, greater absolute risk reductions may have been observed.

This post hoc analysis of APEX demonstrates that extended-duration betrixaban is associated with a significant reduction in fatal or irreversible events as compared with standard-duration enoxaparin. The benefit begins to emerge during the period of parenteral therapy and increases through the period of active treatment at 35 to 42 days as well as the entire duration of follow-up at 77 days. Based on the data from all randomized patients, one would need to treat 65 patients with betrixaban to prevent 1 fatal or irreversible event as compared with enoxaparin. In general, a number needed to treat <100 is considered compelling in clinical practice.

In a traditional net clinical outcomes analysis where efficacy events (including reversible and nonfatal efficacy events such as a positive compression ultrasound for asymptomatic proximal venous thromboembolism) are combined with major bleeding events (many of which are reversible and nonfatal), there is also a benefit in favor of betrixaban. Because major bleeding was not increased with betrixaban, the net benefit associated with the drug is predominantly driven by its improved efficacy. However, a numeric but not significant excess of intracranial hemorrhages in the enoxaparin strategy helped drive the net clinical outcome in favor of betrixaban.

There was a significant reduction in fatal or irreversible events in cohort 1. The full dose of betrixaban (80 mg) was associated with a reduction in fatal or irreversible events, whereas the adjusted dose (40 mg) was not. Furthermore, in patients treated with the full 80-mg dose in cohort 1, there was a robust 2.3% absolute risk reduction (P=0.002), indicating that only 43 patients with positive D-dimer results in cohort 1 would need to be treated with full-dose betrixaban to prevent 1 fatal or irreversible event.

Findings from the ADOPT (Apixaban Dosing to Optimize Protection from Thrombosis) trial did not demonstrate benefit but showed an increase in major bleeding (0.47% versus 0.19%) when comparing apixaban versus enoxaparin, making it impossible to demonstrate a net clinical benefit. Although results from the MAGELLAN (Venous Thromboembolic Event [VTE] Prophylaxis in Medically Ill Patients) trial demonstrated a reduction in the primary end point, this was offset by an increase in fatal bleeding (7 fatal bleeds versus 1 fatal bleed, P=0.034) and an increase in intracranial hemorrhage (2 versus 0, P<0.25), making it difficult to demonstrate a favorable reduction in fatal or irreversible events. Neither ADOPT nor MAGELLAN published analyses of fatal or irreversible end points.

It is notable that death, MI, and stroke, a combined end point often used in “arterial” cardiovascular trials, was reduced in acutely ill medical patients treated with betrixaban, a treatment, which was aimed at reducing “venous” thromboses events.

Limitations

The case report forms did not characterize whether the recurrent MIs were ST-segment elevation myocardial infarctions or non–ST-segment elevation myocardial infarctions, and infarct size of the recurrent MIs was not quantitated. In addition, adjudication was not performed to determine whether there was a segmental versus subsegmental involvement among patients with PE. Finally, this analysis did not use weighted outcomes to incorporate physician and patient preference regarding their perceived import regarding the outcomes.

Conclusions

Among hospitalized medically ill patients, extended-duration betrixaban demonstrates a favorable net clinical outcome and is associated with an ≈30% reduction in fatal or irreversible ischemic or bleeding events compared with standard-duration enoxaparin followed by placebo. A total of 65 patients would require treatment with betrixaban to prevent 1 fatal or irreversible event versus enoxaparin.

Sources of Funding

The study was funded by Portola Pharmaceuticals; APEX ClinicalTrials.gov number NCT01583218. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication. The authors wrote all drafts of the article and take responsibility for its content. The sponsors had the opportunity to review and comment on this article but had no editorial authority.

Disclosures

Dr Gibson has received research grant support and modest consulting support from Portola Pharmaceuticals and Johnson and Johnson. Drs Gold, Goldhaber, Harrington, Hernandez, Hull, and Cohen have received research grant support from Portola.
References

1. Cohen AT, Harrington R, Goldhaber SZ, Hull R, Gibson CM, Hernandez AF, Kitt MM, Lorenz TJ. The design and rationale for the Acute Medically Ill Venous Thromboembolism Prevention with Extended Duration Betrixaban (APEX) study. *Am Heart J*. 2014;167:335–341.

2. Cohen AT, Harrington RA, Goldhaber SZ, Hull RD, Wiens BL, Gold A, Hernandez AF, Gibson CM; Investigators A. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. *N Engl J Med*. 2016;375:534–544.

3. Unger EF. Weighing benefits and risks—the FDA’s review of prasugrel. *N Engl J Med*. 2009;361:942–945.

4. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM; Investigators T-T. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015.

5. Goldhaber SZ, Leizorovicz A, Kakkar AK, Haas SK, Merli G, Knabb RM, Weitz JJ; Investigators AT. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med*. 2011;365:2167–2177.

6. Cohen AT, Spiro TE, Buller HR, Haskell L, Hu D, Hull R, Mebazaa A, Merli G, Schellong S, Spyropoulos AC, Tapson V; Investigators M. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med*. 2013;368:513–523.

DOI: 10.1161/JAHA.117.006015
SUPPLEMENTAL MATERIAL
## Table S1. Sensitivity Analysis for Composite of Fatal or Irreversible Events Using Cochran-Mantel-Haenszel Test

|                  | Through Visit 3 or Day 42 | Through day 77 |
|------------------|---------------------------|----------------|
|                  | Betrixaban               | Enoxaparin     | P-Value* | Betrixaban               | Enoxaparin     | P-Value* |
|                  | no./total no. (%)        | no./total no. (%) |          | no./total no. (%)        | no./total no. (%) |          |
| Composite        |                          |                |          |                          |                |          |
| Cohort 1         | 82/2314 (3.5)            | 111/2313 (4.8) | 0.028    | 101/2314 (4.4)           | 145/2313 (6.3) | 0.003    |
| Cohort 2         | 105/3407 (3.1)           | 139/3391 (4.1) | 0.017    | 133/3407 (3.9)           | 180/3391 (5.3) | 0.004    |
| All Randomized Patients | 109/3759 (2.9) | 153/3754 (4.1) | 0.003    | 137/3759 (3.6)           | 194/3754 (5.2) | 0.001    |
| Composite - 80mg |                          |                |          |                          |                |          |
| Cohort 1         | 56/1828 (3.1)            | 86/1826 (4.7)  | 0.009    | 70/1828 (3.8)            | 112/1826 (6.1) | 0.001    |
| Cohort 2         | 73/2720 (2.7)            | 109/2718 (4.0) | 0.005    | 95/2720 (3.5)            | 140/2718 (5.2) | 0.002    |
| All Randomized Patients | 74/118 (2.5)  | 118/2990 (4.0) | 0.001    | 96/2987 (3.2)            | 149/2990 (5.0) | 0.001    |
| Composite - 40mg |                          |                |          |                          |                |          |
| Cohort 1         | 25/484 (5.2)             | 24/483 (5.0)   | 0.940    | 30/484 (6.2)             | 32/483 (6.6)   | 0.679    |
| Cohort 2         | 30/683 (4.4)             | 29/668 (4.3)   | 0.987    | 36/683 (5.3)             | 39/668 (5.8)   | 0.590    |
| All Randomized Patients | 30/730 (4.1)  | 31/725 (4.3)   | 0.893    | 36/730 (4.9)             | 41/725 (5.7)   | 0.512    |
| Composite - Excluding Non-Fatal PE | | | | | | |
| Cohort 1         | 78/2314 (3.4)            | 96/2313 (4.2)  | 0.151    | 97/2314 (4.2)            | 130/2313 (5.6) | 0.019    |
| Cohort 2         | 98/3407 (2.9)            | 124/3391 (3.7) | 0.055    | 126/3407 (3.7)           | 164/3391 (4.8) | 0.016    |
| All Randomized Patients | 101/3759 (2.7) | 136/3754 (3.6) | 0.014    | 129/3759 (3.4)           | 176/3754 (4.7) | 0.004    |
| Composite - Excluding Non-Fatal PE + MI | | | | | | |
| Cohort 1         | 70/2314 (3.0)            | 89/2313 (3.9)  | 0.119    | 92/2314 (4.0)            | 121/2313 (5.2) | 0.035    |
|                  | Cohort 1 (%) | Cohort 2 (%) | All Randomized Patients (%) |
|------------------|--------------|--------------|-----------------------------|
|                  | 5/17 (2.9)   | 89/3407 (2.6)| 92/3759 (2.5)               |
|                  | 12/224 (5.4) | 115/3391 (3.4)| 127/3754 (3.4)             |
|                  |              |              | 0.048                       |
|                  |              |              | 0.012                       |
|                  | 12/35 (3.4)  | 120/3407 (3.5)| 123/3759 (3.3)             |
|                  |              |              | 0.012                       |
|                  | 12/337 (3.6) | 152/3391 (4.5)| 164/3754 (4.4)             |
|                  |              |              | 0.037                       |

*For cohort 1, treatment and the composite endpoint were stratified by dosing criteria (creatinine clearance ≥15ml and <30 ml/min, receipt of a concomitant pgp inhibitor with severe renal insufficiency, or neither) Cohort 2 and All Randomized Patients stratification was done by dosing criteria and entry criteria (D-dimer ≥2 XULN or <2 XULN)
Table S2. Sensitivity Analysis for Composite of Fatal or Irreversible Events Using All-Cause Death

| Composite*                    | Through Visit 3 or Day 42 | Through day 77 |
|-------------------------------|---------------------------|----------------|
|                               | Betrixaban                | Enoxaparin    | Hazard Ratio | P-Value | Betrixaban | Enoxaparin | Hazard Ratio | P-Value |
|                               | no./total no. (%)         | no./total no. (%) | (95% CI)     |         | no./total no. (%) | no./total no. (%) | (95% CI) |         |
| Cohort 1                      | 128/2314 (5.5)            | 149/2313 (6.4) | 0.86 (0.68, 1.08) | 0.196   | 171/2314(7.4) | 202/2313 (8.7) | 0.85 (0.69, 1.04) | 0.105 |
| Cohort 2                      | 169/3407 (5.0)            | 189/3391 (5.6) | 0.89 (0.72, 1.09) | 0.257   | 227/3407 (6.7) | 255/3391 (7.5) | 0.89 (0.74, 1.06) | 0.182 |
| All Randomized Patients       | 175/3759 (4.7)            | 208/3754 (5.5) | 0.84 (0.69, 1.02) | 0.084   | 235/3759 (6.3) | 277/3754 (7.4) | 0.84 (0.71, 1.01) | 0.057 |

*In this sensitivity analysis, all-cause death has replaced cardiopulmonary death in the composite end point
Table S3. Composite of Fatal and Irreversible Events – Full Dose (80mg)

| Outcome*                  | Through Visit 3 or day 42 | Through day 77 |
|---------------------------|---------------------------|----------------|
|                            | Betrixaban                | Enoxaparin‡    | Betrixaban    | Enoxaparin‡  |
|                            | no./total no. (%)         | no./total no. (%) | no./total no. (%) | no./total no. (%) |
| Cohort 1                   |                           |                |                |
| Composite - n/N (%)        | 56/1828 (3.1)             | 86/1826 (4.7)  | 70/1828 (3.8)  | 112/1826 (6.1) |
| Ischemic Events – n        |                           |                |                |
| Ischemic cardiopulmonary death† | 47                       | 54             | 59             | 73           |
| Nonfatal ischemic stroke  | 4                         | 10             | 5              | 12           |
| Myocardial infarction     | 9                         | 11             | 10             | 15           |
| Nonfatal pulmonary embolism | 2                        | 13             | 2              | 16           |
| Bleed Events – n          |                           |                |                |
| Fatal Bleed               | 0                         | 1              | 0              | 1            |
| Intracranial Hemorrhage   | 0                         | 3              | 0              | 4            |
| Cohort 2                   |                           |                |                |
| Composite                  | 73/2720 (2.7)             | 109/2718 (4.0) | 95/2720 (3.5)  | 140/2718 (5.2) |
| Ischemic Events            |                           |                |                |
| Ischemic cardiopulmonary death | 57                       | 69             | 74             | 90           |
| Nonfatal ischemic stroke  | 7                         | 13             | 8              | 17           |
| Myocardial infarction     | 12                        | 13             | 13             | 17           |
| Nonfatal pulmonary embolism | 4                        | 14             | 4              | 18           |
| Bleed Events               |                           |                |                |
| Fatal Bleed               | 0                         | 1              | 0              | 1            |
| Intracranial Hemorrhage   | 1                         | 5              | 1              | 6            |
| All Randomized Patients   |                           |                |                |
| Composite                  | 74/2987 (2.5)             | 118/2990 (4.0) | 96/2987 (3.2)  | 149/2990 (5.0) |
| Ischemic Events            |                           |                |                |
| Ischemic cardiopulmonary death | 58                       | 77             | 75             | 98           |
| Nonfatal ischemic stroke  | 7                         | 14             | 8              | 18           |
| Myocardial infarction     | 12                        | 14             | 13             | 18           |
| Nonfatal pulmonary embolism | 4                        | 14             | 4              | 18           |
| Bleed Events               |                           |                |                |
| Fatal Bleed               | 0                         | 1              | 0              | 1            |
| Intracranial Hemorrhage   | 1                         | 5              | 1              | 6            |

* Data for safety outcomes were evaluated through visit 3 or day 42. The breakdown of events adds up to more than composite events because composite only includes first event patient experienced. Cohort 1 and Cohort 2 analyses use mITT population.
†Includes fatal PE/VTE - confirmed, fatal PE/VTE - possible, fatal PE/VTE - probable, arrhythmic event, heart failure, fatal ischemic stroke, fatal myocardial infarction, sudden death of unknown cause
‡Enoxaparin was administered for 10 ± 4 days, followed by oral betrixaban placebo for 35 to 42 days
Table S4. Composite of Fatal and Irreversible Events – Reduced Dose (40mg)

| Outcome* | Through Visit 3 or day 42 | Through day 77 |
|----------|---------------------------|----------------|
|          | Betrixaban no./total no. (%) | Enoxaparin† no./total no. (%) | Betrixaban no./total no. (%) | Enoxaparin† no./total no. (%) |
| Cohort 1 |                            |                |                            |                |
| Composite - n/N (%) | 25/484 (5.2) | 24/483 (5.0) | 30/484 (6.2) | 32/483 (6.6) |
| Ischemic Events – n |                |                |                            |                |
| Ischemic cardiopulmonary death† | 20 | 20 | 24 | 26 |
| Nonfatal ischemic stroke | 1 | 1 | 2 | 2 |
| Myocardial infarction | 2 | 1 | 2 | 3 |
| Nonfatal pulmonary embolism | 3 | 3 | 3 | 3 |
| Bleed Events – n |                |                |                            |                |
| Fatal Bleed | 0 | 0 | 0 | 0 |
| Intracranial Hemorrhage | 0 | 0 | 0 | 0 |
| Cohort 2 |                            |                |                            |                |
| Composite | 30/683 (4.4) | 29/668 (4.3) | 36/683 (5.3) | 39/668 (5.8) |
| Ischemic Events |                |                |                            |                |
| Ischemic cardiopulmonary death | 22 | 23 | 27 | 30 |
| Nonfatal ischemic stroke | 1 | 2 | 2 | 3 |
| Myocardial infarction | 2 | 2 | 2 | 5 |
| Nonfatal pulmonary embolism | 4 | 3 | 4 | 3 |
| Bleed Events |                |                |                            |                |
| Fatal Bleed | 1 | 0 | 1 | 0 |
| Intracranial Hemorrhage | 0 | 0 | 0 | 0 |
| All Randomized Patients |                            |                |                            |                |
| Composite | 30/730 (4.1) | 31/725 (4.3) | 36/730 (4.9) | 41/725 (5.7) |
| Ischemic Events |                |                |                            |                |
| Ischemic cardiopulmonary death | 22 | 25 | 27 | 32 |
| Nonfatal ischemic stroke | 1 | 2 | 2 | 3 |
| Myocardial infarction | 2 | 2 | 2 | 5 |
| Nonfatal pulmonary embolism | 4 | 3 | 4 | 3 |
| Bleed Events |                |                |                            |                |
| Fatal Bleed | 1 | 0 | 1 | 0 |
| Intracranial Hemorrhage | 0 | 0 | 0 | 0 |

* Data for safety outcomes were evaluated through visit 3 or day 42. The breakdown of events adds up to more than composite events because composite only includes first event patient experienced. Cohort 1 and Cohort 2 analyses use mITT population.
†Includes fatal PE/VTE - confirmed, fatal PE/VTE - possible, fatal PE/VTE - probable, arrhythmic event, heart failure, fatal ischemic stroke, fatal myocardial infarction, sudden death of unknown cause
‡Enoxaparin was administered for 10 ± 4 days, followed by oral betrixaban placebo for 35 to 42 days
Figure S1. Study Design

- Subjects enrolled (N=7513)
- Double blind, double dummy

- **Standard Prophylaxis**
  - 10 + 4 days

- **Extended Prophylaxis**
  - 35 – 42 days

- **Evaluation**

- **Enoxaparin**
  - 40 mg

- **Placebo**

- **Betrixaban**
  - 80 mg

- **Betrixaban**
  - 80 mg

- **Ultrasound & Visit 3**
  - Day 35 (+7 days)

- **Follow-up safety visit**
  - 30 Days After Visit 3 (+5 days)

Loading dose 160 mg
Figure S2. Study Population Flowchart

All Patients Randomized  
N = 7,513

mITT Patients  
At Least 1 Dose of Study Drug  
N = 7,441

Betrixaban Arm  
N = 3721

Enoxaparin Arm  
N = 3720

Cohort 2  
D-dimer ≥ 2 x ULN or age ≥ 75  
N = 3407

Cohort 1  
D-dimer ≥ 2 x ULN  
N = 2314

Cohort 2  
D-dimer ≥ 2 x ULN or age ≥ 75  
N = 3391

Cohort 1  
D-dimer ≥ 2 x ULN  
N = 2313
Figure S3. Time-to-First Fatal or Irreversible Event Excluding Non-Fatal PE in Cohort 1

**Through Visit 3**
- HR = 0.81 (95% CI: 0.60, 1.09)
- ARR = 0.78%
- NNT = 128

**Through End of Trial**
- HR = 0.75 (95% CI: 0.58, 0.97)
- ARR = 1.26%
- NNT = 79

*End of Trial defined as final follow-up visit (30 + 5 days after Visit 3)*

Note: Enoxaparin was administered for 10 ± 4 days, followed by oral betrixaban placebo for 35 to 42 days.
Figure S4. Time-to-First Fatal or Irreversible Event Excluding Non-Fatal PE in the All Randomized Population

*End of Trial defined as final follow-up visit (30 + 5 days after Visit 3)
Note: Enoxaparin was administered for 10 ± 4 days, followed by oral betrixaban placebo for 35 to 42 days
**Figure S5. Time-to-First Fatal or Irreversible Event in Cohort 1 – Full Dose (80mg)**

*End of Trial defined as final follow-up visit (30 + 5 days after Visit 3)*

Note: Enoxaparin was administered for 10 ± 4 days, followed by oral betrixaban placebo for 35 to 42 days
Figure S6. Time-to-First Fatal or Irreversible Event in the All Randomized Population – Reduced Dose (40mg)

Through Visit 3
- HR = 0.95 (95% CI: 0.58, 1.58)
- ARR = 0.17%
- NNT = 588

Through End of Trial*
- HR = 0.87 (95% CI: 0.56, 1.37)
- ARR = 0.73%
- NNT = 137

*End of Trial defined as final follow-up visit (30 + 5 days after Visit 3)

Note: Enoxaparin was administered for 10 ± 4 days, followed by oral betrixaban placebo for 35 to 42 days
Figure S7. Time-to-First CV Death, MI or Stroke in the All Randomized Population

Through Visit 3
HR = 0.73 (95% CI: 0.55, 0.96)
ARR = 0.85%
NNT = 85

Through End of Trial*
HR = 0.75 (95% CI: 0.59, 0.96)
ARR = 0.99%
NNT = 101

*End of Trial defined as final follow-up visit (30 + 5 days after Visit 3)
Note: Enoxaparin was administered for 10 ± 4 days, followed by oral betrixaban placebo for 35 to 42 days
Appendix: APEX Investigators (No. of patients enrolled in each country, No. of sites):

Argentina (215 patients, 7 sites): F. Bello, A.E. Ferrari, H. Jure, S. Macin, M. Oliva, M. Parody, C. Poy;

Australia (20 patients, 5 sites): R. Baker, D. Colquhoun, P. Couglin, S. Finger, G. Hammerschlag, A. Rubinfeld;

Austria (15 patients, 5 sites): K. Huber, J. König, R. Mathies, E. Pilger, H. Schoenerr;

Belarus (69 patients, 7 sites): I. Adzerikho, V. Koryk, E. Mikhailova, N. Mitkovskaya, S. Pimanov, L. Polonetsky, N. Soroka;

Belgium (15 patients, 5 sites): D. Blockmans, M. Delforge, A. Dive, F. Lienart, S. Motte;

Brazil (57 patients, 8 sites): J. Annichino Bizzacchi, E. Fiss, A. Freire, E. Manenti, E. Ramacciotti, S. Raymuno, A. Rocha, J.F. Saraiva;

Bulgaria (431 patients, 15 sites): B. Dimov, M. Grigorov, R. Kalpachki, Z. Kamenova, M. Kostadinova, M. Milanova, V. Mincheva, G. Pencheva, D. Raev, N. Runev, N. Stoeyva, M. Stoyanov, S. Syulemzova, G. Todorov, M. Tokmakova;

Canada (51 patients, 7 sites): A. Dhar, J. Douketis, S. Kahn, G. Le Gal, M. Pearce, S. Provencher, S. Verreault;

Chile (44 patients, 4 sites): M. Arias Alarcon, C. Oliva, M. Opazo Lazcano, S. Potthoff Cardenas;

Croatia (92 patients, 11 sites): S. Butkovic-Soldo, S. Car, N. Ciglenecki, I. Francetic, M. Jakopovic, H. Kalinic-Grgoricin, A. Knezevic, B. Malojcic, S. Marusic, J. Sikic Vagic, V. Skerk;

Czech Republic (237 patients, 22 sites): O. Cermak, P. Červinka, J. Chlumsky, J. Chochola, V. Cizek, M. Dunaj, J. Dusek, L. Francek, J. Havelka, M. Herold, R. Holaj, I. Horny, J. Hubac, P. Hajner, P. Kolman, P. Lang, O. Mayer, J. Mikulova, I. Podpera, P. Reiterer, R. Spacek, J. Vejvoda, M. Vyhnanek;

Denmark (12 patients, 5 sites): H. Christensen, M. Lassen, M. Storgaard, C. Tuxen, S. Urhammer;

Estonia (205 patients, 3 sites): M. Lember, T. Marandi, T. Uuetoa;

Finland (26 patients, 7 sites): J. Airaksinen, J. Honkaniemi, R. Kaaja, R. Lassila, J. Saarinen, T. Tatlisumak, S. Vikman;

France (293 patients, 25 sites): B. Agraou, S. Aquilanti, A. Belhassane, D. Brisot, G. De Geeter, P. Debourdeau, E. Decoulx, D. El Kouri, N. Falvo, C. Grange, P. Lacroix, E. Messas, P. Mismetti, K. Montaclair, D. Mottier, N. Paleiron, L. Payot, G. Pernod, P. Pottier, A. Proust, I. Quere, P-M. Roy, J. Schmidt, G. Simoneau;

Georgia (260 patients, 8 sites): I. Datikashvili-David, G. Khabeshvili, I. Khintibidze, B. Kobulia, I. Megreladze, Z. Pagava, K. Paposhvili, T. Shaburishvili;

Germany (196 patients, 20 sites): B. Amann, J. Berrouchot, J. Beyer-Westendorf, E. Blessing, M. Böttger, T. Dengler, C. Diehm, R. Dziallas, S. Genth-Zotz, F. Hamann, T. Horacek, S. Klimpe, R. Kröning, H. Lapp, M. Licka, T. Rizos, S. Schellong, J. Schmidt-Lucke, C. Singer, C. Tiefenbacher, R. Veltkamp, C. Weimar, U. Zeymer;

Hungary (252 patients, 20 sites): B. Alkonyi, J. Faluközy, L. Futo, A. Katona, R. Kirschner, P. Kristóf, F. Lakatos, Z. Laszlo, G. Lupkovics, B. Mekely, C. Nagy András, L. Németh, A. Papp, P. Soltesz, Z. Sudár, G. Szabo, N. Szegedi, G. Timár, J. Valocí, A. Vertes;

Israel (99 patients, 8 sites): S. Efrati, M. Elias, A. Gafter, T. Hayek, O. Hussein, H. Lishner, G. Lugassy, D. Zeltser;

Italy (261 patients, 19 sites): W. Ageno, I. Cerveri, A. D’Angelo, A. De Pellegrin, D. Imberti, R. Landolfi, G. Lembo, C. Lodigiani, M. Luijetti, M. Moia, M. Molteni, N. Mumoli, S. Novo, F. Orlandini, R. Parisi, A. Pizzini, F. Pomero, A. Salvi, A. Schenone, A. Visinà;

Latvia (319 patients, 5 sites): D. Krievins, V. Martinova, N. Pontaga, V. Rozítis, I. Stukena;

Lithuania (470 patients, 12 sites): B. Alekniene, A. Bagdonas, V. Basiokieni, Z. Butkiene, V. Griskeviciene, A. Naudziunas, R. Norvaisieni, R. Norvilieni, R. Petrauskiene, R. Poskieni, D. Susinskieni, A. Valavicius;

Peru (152 patients, 7 sites): R. Castillo Leon, R. Cotrina Pereyra, L. Farjardo Karlo, M. Horna, J. Lema Osores, M. Salas, L. Toche Yañez;

Poland (369 patients, 16 sites): W. Fryze, Z. Gaciong, J. Gniot, D. Gorecka, P. Gruenpeter, P. Grzelakowski, D. Jastrzebski, L. Kucharski, E. Mirek-Brynska, G. Pulkowski, B. Sobkowicz, P. Sulik, W. Tomkowski, L. Walasek, K. Waldekar, K. Wrzesinski;

Romania (170 patients, 10 sites): Z.E. Balogh, M. Bojinca, I. Cerveri, A. D’Angelo, A. De Pellegrin, D. Imberti, R. Landolfi, G. Lembo, C. Lodigiani, M. Luijetti, M. Moia, M. Molteni, N. Mumoli, S. Novo, F. Orlandini, R. Parisi, A. Pizzini, F. Pomero, A. Salvi, A. Schenone, A. Visonà;

Russia (971 patients, 37 sites): A. Abashev, D. Andreiev, K. Apartsin, M. Arkhipov, O. Averkov, O. Barbarash, G. Bolskaya, E. Bogdanov, S. Boldueva, Z. Chefranova, Y. Dovgalevskiy, O. Ershova, B. Goloshchekin, N. Khachatryan, E. Khurs, G. Klein, Z. Kolabala, E. Kosmacheva, V. Kostenko, A. Malygin, T. Martynenko, V. Martynenko, N. Maslova, V. Mordovin, K. Nikolaev, R. Nilk, E. Panchenko, D. Popov, E. Privalova, O. Reshetko, E. Sergeeva, Y. Shapovalova, L. Shpagina, Y. Shvarts, V. Simanenkov, O.
Solovyov, E. Vishneva, A. Vishnevskiy; **Serbia (115 patients, 5 sites):** S. Apostolovic, V. Celic, S. Ilie, A. Kovacevic-Kuzmanovic, V. Miloradovic; **Singapore (1 patient, 1 site):** R.S. Tan; **Slovak Republic (105 patients, 11 sites):** S. Bodikova, A. Cervenakova, M. Dvorak, L. Gaspar, O. Herman, A. Hrubon, M. Kokles, G. Krastev, J. Payer, D. Prokop, M. Spisakova; **South Africa (91 patients, 7 sites):** D. Adler, M. Basson, J. Breedt, J. Engelbrecht, B. Jacobson, I. Mitha, C. Van Dyk; **Spain (412 patients, 18 sites):** L.A. Alvarez Sala, C. Barbagelata López, J. Bisbe, A. Castro Guardiola, J.M. Cepeda, F. Cereto, E. Diaz Santos, R. Ferrer, J. Gomez Cerezo, J.R. Gonzales-Porras, J. Grandes, D. Jiménez, I. Martín Loeches, L. Mellibovsky, C. Richart, A. Riera, J. Trujillo, J.A. Vargas Nunez, J. Villalta; **Turkey (54 patients, 12 sites):** O. Akgul, S. Guneri, K. Kilichesmez, C. Kırma, H. Kutluk, B. Nazliel, G. Okumus, G. Ongen, K. Tigen, M. Topcuoglu, E. Tuncay; **Ukraine (886 patients, 31 sites):** O. Abrahamovyč, V. Batushkin, J. Brozhyk, I. Burmak, O. Godlevska, A. Goloborodko, B. Goloborodko, Y. Goncharova, V. Gryb, O. Karpenko, M. Kopytsya, V. Koshlia, O. Krakhmalova, I. Kyrchenko, O. Legkonogov, Y. Malynovskyk, V. Maslovskiy, V. Nikonor, O. Parkhomenko, M. Perepeliuk, D. Reshotko, L. Rudenko, T. Ryabichenko, I. Svyrivod, Y. Vyshchenko, V. Tseluyko, G. Ursol, I. Vakaliuk, I. Vishnivetsky, L. Voronkov, A. Yagensky; **United Kingdom (22 patients, 5 sites):** R. Body, D. Chandra, M. Davis, P. Kesteven, P. MacCallum, C. McCollum, I. Natarajan; **USA (527 patients, 68 sites):** E. Almasri, M. Amin, C. Anderson, S. Baker, J. Barney, B. Barth A. Bastani, P. Bercz, M. Bidair, T. Carman, H. Chang, C. Clark, M. Concha, J. Cornell, R. Dhirga, A. Doshi, R. Ebrahimi, B. Farley, G. Fermann, G. Foster, J. Fraiz, J. Fulmer, H. Gaggin, D. Goytia-Leos, B. Hahn, A. Haidar, A. Hamad, M. Hazelrigg, O. Ioachimescu, B. Johnson, H. Kabler, C-K. Kao, M. Kazimir, F. Kouras, M. Kung, R. Lerner, J. Lopez, A. Macchiavelli, S. Mahal, B. Margolis, G. McLaren, T. Milling Jr., M. Mittal, V. Nadar, V. Ohaju, T. Orté, J. Overcash, K. Parthiban, R. Pearl, L. Pineda, R. Pratt, J. Pullman, O. Quintana, R. Rajan, P. Rastogi, C. Rees, W. Rodriguez, F. Saba, N. Shammas, S. Sharma, S. Sokol, S. Stoltz, D. Subich, M. Tuck, J. Updegrove, A. Warner, M. Welch, J. Welker, B. Whitman, T. Wichman, K. Youssef, R. Yusen, N. Zakai.