MEDICALLY ILL HOSPITALIZED PATIENTS FOR COVID - THROMBOSIS EXTENDED PROPHYLAXIS WITH RIVAROXABAN THERAPY

On Behalf of The Michelle Trial Investigators
### DECLARATION OF INTEREST

**FOR EDUARDO RAMACCIOTTI**

<table>
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<tr>
<th>Category</th>
<th>Details</th>
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<td><strong>RESEARCH SUPPORT/P.I.</strong></td>
<td>BMS/PFE, BAYER, MCTI</td>
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<tr>
<td><strong>EMPLOYEE</strong></td>
<td>No relevant conflicts of interest to declare</td>
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<tr>
<td><strong>CONSULTANT</strong></td>
<td>No relevant conflicts of interest to declare</td>
</tr>
<tr>
<td><strong>MAJOR STOCKHOLDER</strong></td>
<td>No relevant conflicts of interest to declare</td>
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<td><strong>SPEAKERS BUREAU</strong></td>
<td>BMS/PFE, ASPEN, BAYER, Daiichi-Sankyo, BIOMM</td>
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<td><strong>HONORARIA</strong></td>
<td>No relevant conflicts of interest to declare</td>
</tr>
<tr>
<td><strong>SCIENTIFIC ADVISORY BOARD</strong></td>
<td>BMS/PFE, BAYER, Daiichi-Sankyo</td>
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The **MICHELLE** trial was funded by an unrestricted research grant from **Bayer S.A.**
The devastating Coronavirus disease (COVID-19) pandemic is associated with a high prothrombotic state.\(^1\)

It is unclear if the coagulation abnormalities occur because of the direct effect of SARS-CoV-2 or indirectly by the cytokine storm and endothelial damage or by a combination of mechanisms.\(^2\)

There is a clear indication of in-hospital pharmacological thromboprophylaxis for every patient with COVID-19 after bleed risk assessment.\(^3\)

However, there is much debate regarding the best dosage regimen, and there is no consensus on the role of extended thromboprophylaxis.\(^4\)

Current antithrombotic statements are conflicting for the need (or not) for post-hospital discharge thromboprophylaxis in hospitalized COVID-19 patients.\(^5\)

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MARINER Evaluated Rivaroxaban Versus Placebo for Prophylaxis of VTE After Hospital Discharge in Acutely Medically Ill Patients

**Objective** (Safety and efficacy of rivaroxaban compared with placebo for the prevention of symptomatic VTE and VTE-related death post hospital discharge in high-risk acutely medically ill patients)

**Population**
Acute medically ill patients at high risk of VTE after hospital discharge who had already been anticoagulated with UFH/LMWH

**Design**
Multicenter, prospective, randomized, double-blind, placebo-controlled, event-driven study

**PPVJ02-14**
Study comparing Rivaroxaban to Placebo for VTE prevention in acutely medically ill patients

*Patients with GCS <10 or >31 were excluded. **Hospitalization period of 3 consecutive days. Risk of VTE defined as Pharmacological score 2 or 3 plus 3-derivation level in CMR score.

\[ \text{HR}=0.44 \ (95\% \ CI \ 0.22-0.89) \]

Rivaroxaban
Placebo

\[ \text{HR}=0.93 \ (95\% \ CI \ 0.62-1.42) \]

\[ p=0.14 \]

VTE-Related Death Rates with Rivaroxaban Were Not Significantly Different vs Placebo
Cumulative event rates for composite of symptomatic VTE or VTE-related death (**)

**Significant Reduction of Symptomatic VTE with Rivaroxaban After Discharge in Acutely Medically Ill Patients**

**Objective** (Evaluation of Rivaroxaban for the prevention of symptomatic VTE and VTE-related death after hospital discharge in acutely medically ill patients)

**Population**
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\[ \text{HR}=0.42 \ (95\% \ CI \ 0.22-0.89) \]

Rivaroxaban
Placebo

\[ \text{HR}=0.18 \ (95\% \ CI \ 0.10-0.32) \]

\[ p=0.14 \]

VTE-Related Death Rates with Rivaroxaban Were Not Significantly Different vs Placebo
Cumulative event rates for VTE-related death (**)

Spyropoulos A et al, N Engl J Med 2018
56% symptomatic VTE
NoBleeds
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COLLABORATION

Bayer [*]

[*] Unrestricted research grant from Bayer S.A., which was not involved in design, conduct or interpretation of the study
**MICHELLE STUDY DESIGN**

**Design:** Prospective, randomized, open-label, controlled, multi-center trial

- **Rivaroxaban**
  - 10 mg/day (CrCl ≥ 30ml/min)

- **No intervention**

- **Discharge**
- **Screening**

- **Treatment**

- **Follow-up**
  - Day 35±4
  - Day 75 (phone call)

- **Doppler US + pulmonary angioCT at day 35±4**

**Primary endpoint:** symptomatic VTE, VTE-related death, VTE detected by mandatory bilateral lower limbs venous duplex scan and pulmonary angioCT on day 35±4 post-hospital discharge and (myocardial infarction [MI], non-hemorrhagic stroke, major adverse limb events [MALE] and cardiovascular [CV] death + all cause death up to day 35±4 post-hospital discharge.

**Power:** 80%, Two sided alpha 0.05 (Control 15%, Treatment 5% 60% RRR)

ESC CONGRESS 2021
THE DIGITAL EXPERIENCE
KEY INCLUSION AND EXCLUSION CRITERIA

KEY INCLUSION CRITERIA

- Patients ≥ 18 years hospitalized for minimum of 3 days with standard dose thromboprophylaxis (LMWH, fondaparinux or UFH) prior to randomization for SARS-CoV-2 infection (COVID-19)
- Total modified IMPROVE VTE Risk Score ≥ 4 OR total modified IMPROVE VTE Risk Score 2 or 3 and D dimer > 500 ng/ml during index hospitalization

KEY EXCLUSION CRITERIA

- Bleeding Risks
  - Any bleeding within 3 months
  - Surgery, biopsy or trauma 4 weeks prior or planned
  - Active gastroduodenal ulcer
  - Active cancer
- Required anticoagulation after discharge
- Use of dual antiplatelet therapy during the index hospitalization
- Creatinine clearance < 30 ml/min
- Concomitant Medications
  - Combined P-gp and strong CYP3A4 inhibitors
  - Combined P-gp and strong CYP3A4 inducers
<table>
<thead>
<tr>
<th>VTE RISK FACTOR</th>
<th>POINTS</th>
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<tr>
<td>Previous VTE</td>
<td>3</td>
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<tr>
<td>Known thrombophilia</td>
<td>2</td>
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<tr>
<td>Lower-limb paralysis</td>
<td>2</td>
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<tr>
<td>History of cancer (*)</td>
<td>2</td>
</tr>
<tr>
<td>Immobilization ≥1 day (*)</td>
<td>1</td>
</tr>
<tr>
<td>ICU/CCU stay</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;60 years</td>
<td>1</td>
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<tr>
<td>D dimer ≥ 2X UNL</td>
<td>2</td>
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</tbody>
</table>

(*) Modified for the MARINER clinical trial | ICU = intensive care unit; CCU = critical care unit.
PRIMARY OUTCOME
Composite of symptomatic VTE, VTE-related death, and VTE detected at bilateral lower limbs venous duplex scan and computed tomography pulmonary angiogram and symptomatic arterial thromboembolism (myocardial infarction [MI], non-hemorrhagic stroke, major adverse limb event [MALE], and cardiovascular [CV] death at day 35.

KEY SAFETY OUTCOME
Incidence of major bleeding according to ISTH criteria.

SECONDARY OUTCOME
A composite of MI, stroke, arrhythmias, heart failure, VTE, and all-cause death.

Endpoints were adjudicated by a blinded independent committee.
Power of 80% and $\alpha = 0.05$

Anticipated occurrence of the primary efficacy endpoint of 15% in the control group and 5% of the treatment group (RRR = 67%).

If there is a true difference in favor of the proposed treatment of 10% (15% vs. 5%), then 282 patients were required.

With a drop-out rate of 10%, a total of 320 patients was necessary (160 per arm).

The primary analysis was performed using the intention-to-treat principle.
RANDOMIZED (N=320)

Allocated to rivaroxaban (n=160)
- Received allocated intervention (n=158)
  - Did not receive allocated intervention (n=2)
    - 1 patient allocated to another study
    - 1 patient prolonged hospitalization

Lost to follow-up (n=1)
  Discontinued intervention
  Patient decision to discontinue

Allocated to no anticoagulation (n=160)

Lost to follow-up (n=2)
  Patient did not return contact
  Withdrawn informed consent (n=1)

Analyzed (n=157)
  Intention-to-treat-analysis
  AngioCT scans available = 114 (73%)
  Doppler US available = 134 (85%)

Analyzed (n=157)
  Intention-to-treat-analysis
  AngioCT scans available = 90 (57%)
  Doppler US available = 118 (75%)
## BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>RIVAROXABAN (N=157)</th>
<th>CONTROL (N=157)</th>
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<tbody>
<tr>
<td>Mean age (yr) – mean (SD)</td>
<td>57.73 (14.64)</td>
<td>56.21 (15.57)</td>
</tr>
<tr>
<td>Age ≥ 75 yr – n (%)</td>
<td>17 (10.8%)</td>
<td>15 (9.6%)</td>
</tr>
<tr>
<td>Female sex – n (%)</td>
<td>62 (39.5%)</td>
<td>64 (40.8%)</td>
</tr>
<tr>
<td>BMI – mean (SD)</td>
<td>29.55 (5.60)</td>
<td>29.94 (6.08)</td>
</tr>
<tr>
<td>Creatinine Clearance ml/min – n/total (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 to &lt;50 ml/min</td>
<td>4/157 (2.5%)</td>
<td>3/155 (1.9%)</td>
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<tr>
<td>≥50 ml/min</td>
<td>153/157 (97.5%)</td>
<td>152/155 (98.1%)</td>
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<tr>
<td>Mean duration of index hospitalization – days – mean (SD)</td>
<td>16.48 (46.97)</td>
<td>12.54 (28.69)</td>
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<tr>
<td>ICU or CCU stay – n (%)</td>
<td>84 (53.5%)</td>
<td>78 (49.7%)</td>
</tr>
<tr>
<td>Enoxaparin 40 mg use – n (%)</td>
<td>134 (85.4%)</td>
<td>137 (87.3%)</td>
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<tr>
<td>Modified IMPROVE VTE risk score – n (%)</td>
<td></td>
<td></td>
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<tr>
<td>2-3</td>
<td>132 (85.4%)</td>
<td>137 (87.3%)</td>
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<tr>
<td>≥4</td>
<td>23 (14.6%)</td>
<td>20 (12.7%)</td>
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<tr>
<td>D-Dimer level above the UNL during index hospitalization – n/total (%)</td>
<td>105/114 (92.1%)</td>
<td>107/116 (92.2%)</td>
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<tr>
<td>Antiplatelets use – n (%)</td>
<td>8 (5.1%)</td>
<td>8 (5.1%)</td>
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**EFFICACY OUTCOMES**

**Primary endpoint***
- Symptomatic + Fatal VTE
  - Control: 8,92%
  - Rivaroxaban: 3,18%
  - RRR = 64%

**Secondary endpoint**
- Control: 8,91%
- Rivaroxaban: 5%
- RRR = 88%

*Composite of symptomatic VTE, VTE-related death, asymptomatic VTE (Doppler and AngioCT scan) and symptomatic ATE, MI, non-hemorrhagic stroke, (MALE), and cardiovascular death at day 35; ** MI, stroke, arrhythmias, heart failure, VTE, and all-cause death
SAFETY OUTCOMES

VERY SMALL NUMBERS, EQUAL BETWEEN GROUPS (P > 5%)

Comparison of major bleeding and major CRNM + all bleeding between Control and Rivaroxaban.
### RISKS & BENEFITS

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<th>Risk Category</th>
<th>Value</th>
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<td>NNT for primary outcome</td>
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<td>NNT for symptomatic + fatal VTE</td>
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<td>NNT for PE+cardiovascular death</td>
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<td>NNH</td>
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CONCLUSION

Thromboprophylaxis with rivaroxaban 10 mg once-daily for 35 days after hospitalization for COVID-19 in patients with high IMPROVE score (2-3 with elevated D-dimer levels or ≥4) improved clinical outcomes, including VTE and VTE-related death, without increasing bleeding compared with no out-of-hospital anticoagulation.
ACKNOWLEDGMENTS

Thank you to Science Valley Research Institute, Bayer Brazil team, investigators, hospitals, study coordinators, DSMB, CEC, core-lab, and study participants who made the MICHELLE trial possible.

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