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DRIVING INNOVATION IN CARDIOVASCULAR DISEASE WITH DABIGATRAN ETEXILATE

Boehringer Ingelheim

Boehringer Ingelheim is dedicated to conducting and supporting research in areas of significant unmet medical need. As part of Boehringer Ingelheim's commitment to furthering physician understanding and patient care in stroke prevention and cardiology, a number of new global studies are being undertaken to investigate the potential of dabigatran etexilate in new areas. These new studies form part of the extensive RE-VOLUTION® clinical trial programme for dabigatran etexilate which will involve over 60,000 patients worldwide.[1-14]

New studies with dabigatran etexilate

	RE-DUAL PCI™ Study in NVAF patients undergoing PCI	RE-SPECT ESUS™ Study of secondary stroke prevention in ESUS patients	RE-CIRCUIT® Study of peri-procedural anticoagulation in AF ablation
	Randomized **E**valuation of **DUAL** antithrombotic therapy with dabigatran etexilate vs. triple antithrombotic therapy with warfarin in patients with NVAF that have undergone **PCI** with stenting[12]	**R**andomized **E**valuation in **S**econdary stroke **P**revention Comparing the **E**ffica**C**y and safety of the oral **T**hrombin inhibitor dabigatran etexilate versus acetylsalicylic acid (ASA) in **E**mbolic **S**troke of **U**ndetermined **S**ource* (ESUS)[13]	**R**andomized **E**valuation of dabigatran etexilate **C**ompared to warfar**I**n in pulmona**R**y vein ablation: assessment of different peri-pro**C**ed**U**ral ant**I**coagulation s**T**rategies[14]
MEDICAL NEED	• Percutaneous Coronary Intervention (PCI), also known as angioplasty of the heart vessel, is a medical procedure where stents are used to widen arteries of the heart to restore or improve blood flow[15] • Non-valvular atrial fibrillation (NVAF) patients who undergo PCI with stenting are at increased risk of serious complications caused by blood clots[16,17] • In these patients, long-term treatment, which involves a combination of various antithrombotic therapies, is essential for reducing the risk of developing clots. However antithrombotic therapies are linked to an increased risk of bleeding[18] • A double antithrombotic therapy (with an oral anticoagulant plus one antiplatelet therapy) could reduce the risk of the chance of blood clots and be associated with a lower risk of bleeding in comparison to triple antithrombotic therapy	• Embolic strokes occur when a blood clot forms somewhere in the body and travels through the bloodstream to the brain[19] • Patients who experience ESUS are at increased risk of suffering another stroke with potentially devastating consequences, including high rates of complications and morbidity[20,21] • Limited knowledge exists to help physicians make confident treatment decisions for secondary stroke prevention in ESUS patients[20,22]	• Ablation is a routine, minimally invasive procedure which is conducted to normalise the heart rhythm[23] • Ablation temporarily increases patients' risk of blood clots and stroke[24] • For patients treated with an oral anticoagulant, guidelines recommend undertaking catheter ablation on continuous anticoagulation with warfarin. Data regarding the specific use of non-vitamin K antagonist oral anticoagulants (NOACs), during ablation procedures are lacking[24,25]
AIM	The RE-DUAL PCI™ study aims to advance medical knowledge, guide antithrombotic treatment choice and establish a new standard of care to provide the greatest benefit to patients with NVAF undergoing PCI with stenting[26]	The RE-SPECT ESUS™ study aims to address the current knowledge and treatment gap in secondary prevention of stroke in ESUS patients[13]	The RE-CIRCUIT™ study aims to optimise patient care, simplify management and provide beneficial alternatives to standard anticoagulation with warfarin for patients with NVAF undergoing ablation[14]

	RE-DUAL PCI™ Study in NVAF patients undergoing PCI	RE-SPECT ESUS™ Study of secondary stroke prevention in ESUS patients	RE-CIRCUIT® Study of peri-procedural anticoagulation in AF ablation
STUDY DESIGN	RE-DUAL PCI™ will compare the efficacy and safety of dual antithrombotic therapy with dabigatran etexilate (110mg or 150mg twice daily) plus clopidogrel or ticagrelor versus the currently recommended standard triple antithrombotic therapy regimen with warfarin (INR 2-3) plus clopidogrel or ticagrelor plus acetylsalicylic acid (ASA)[12] RE-DUAL PCI™ is a prospective, randomised, controlled, open-label blinded endpoint (PROBE), event driven study[12]	RE-SPECT ESUS™ will compare the efficacy and safety of dabigatran etexilate (150mg or 110mg twice daily) versus ASA 100mg once daily[13] RE-SPECT ESUS™ is a randomised, double-blind, placebo-controlled study[13]	RE-CIRCUIT™ will explore the safety and efficacy of uninterrupted dabigatran etexilate therapy (150mg twice daily) versus uninterrupted warfarin (INR 2-3) in patients with atrial fibrillation (AF) who undergo ablation[14,26] RE-CIRCUIT™ is a prospective, randomised, open label, blinded endpoint adjudication, controlled study[26]
PATIENTS	8,500 patients with NVAF who have undergone PCI with stenting[26]	6,000 patients diagnosed with ESUS within the 3 months prior to randomisation (6 months in patients ≥60 years and older and with an additional risk factor)[13]	Approximately 700 patients with either paroxysmal or persistent AF, who are scheduled to undergo an ablation procedure[14]
REGIMEN	The study is event driven: all patients will remain in the study until the required number of events has occurred. Individual patient participation will vary from approximately 6 months to 2.5 years or longer (estimated average duration 18 months). Follow up visits every 3 months[26]	Treatment is given for at least 6 months and up to 3 years[13] Major outcomes assessed up to 30 days after the end of treatment[26]	Treatments administered between 4 to 8 weeks prior to the ablation procedure[26] Patients continue treatment for 60 days with follow-up on days 30 and 60[14]
ENDPOINTS	EFFICACY: Time to first thrombotic event (death, myocardial infarction, stroke and systemic embolism)[12] SAFETY: Time to first major bleeding[12]	PRIMARY EFFICACY: Time to first occurrence of recurrent stroke (ischaemic, haemorrhagic or unspecified)[13] PRIMARY SAFETY: Time to first occurrence of major bleed[13]	SAFETY: Major bleeding at 2 months post-procedure[14]
KEY DATES	Start: 2014[12] Estimated date of completion: 2017[12]	Start: 2014[26] Estimated date of completion: 2017/ 2018[26]	Start: 2015[14] Estimated date of completion: 2016[14]
	**Dabigatran etexilate is not approved for patients with ESUS or patients requiring PCI.* *The new study announcements contained within this factsheet have not received indication approvals.*		

Assessing dabigatran in the real-world clinical setting

The introduction of the non-vitamin K antagonist oral anticoagulants has changed prescribing behaviour and drug usage patterns worldwide.[27] Boehringer Ingelheim is undertaking two observational studies to understand how dabigatran is being used in the real-world clinical setting and impacting patient outcomes.[26,28]

GLORIA™-AF is the largest, global observational study collecting real-world data on the use of anticoagulants in patients with atrial fibrillation (AF). The registry will examine physicians' actual prescribing behaviours in treating AF, as well as the factors behind their prescribing decisions.[28]

GLORIA™-AF will collect long-term effectiveness and safety data on a range of anticoagulants, including warfarin, acetylsalicylic acid (ASA) and non-vitamin K antagonist oral anticoagulants for stroke prevention in AF, as well as patient outcomes data.[28] The registry will enrol up to 56,000 patients newly diagnosed with AF at risk of stroke from up to 2,200 sites in nearly 50 countries.[27] Patient enrolment into the registry program has now commenced in all major regions of the world with over 20,000 patients already participating in the registry.[26] The results of GLORIA™-AF are expected to advance current and future management of AF.

In 2015, Boehringer Ingelheim plans to initiate RE-COVERY DVT/PE™, a new global observational study on the management of blood clots in the legs (deep vein thrombosis, DVT) and in the lungs (pulmonary embolism, PE).[26] RE-COVERY DVT/PE™ will provide insight into how the results from previously published dabigatran clinical trials in DVT and PE have impacted real-world clinical practice, and generate further evidence on the effectiveness and safety of the two approved doses of dabigatran (150mg and 110mg twice daily) compared to the vitamin K antagonist warfarin when routinely prescribed by physicians.[26]

RE-COVERY DVT/PE™ will involve up to 14,000 patients worldwide and will provide real-world data on the use of anticoagulants in acute DVT and PE treatment.[26]

Ongoing development of idarucizumab* – the specific reversal agent to dabigatran etexilate

To advance anticoagulation care, Boehringer Ingelheim developed idarucizumab*, a specifically targeted reversal agent to dabigatran for use in rare emergency situations when patients require urgent reversal of its anticlotting effect.[7] Idarucizumab* is currently the only specific reversal agent for a NOAC in regulatory review.[26] In February and March 2015 idarucizumab* was submitted under an accelerated approval pathway to the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and Health Canada for use in dabigatran-treated patients who require urgent anticoagulant reversal.[29] The FDA granted both Breakthrough Therapy and Orphan Drug Designation.[30,31] Boehringer Ingelheim plans to submit idarucizumab* in all countries where dabigatran is licensed.[26] Further regulatory submissions are ongoing and accelerated processes will be pursued with regulatory authorities where available.[26]

- Data from Phase I studies have shown that a 5 minute infusion of idarucizumab* (>2g) led to immediate, complete and sustained reversal of dabigatran in healthy volunteers as well as in elderly and renally-impaired individuals.[32,33] No clinically relevant side effects were identified and idarucizumab* did not over-activate clot production (a pro-coagulant effect).[32,33]

** Idarucizumab is the recommended International Nonproprietary Name (INN). Idarucizumab is an investigational drug, which has not been approved for clinical use, and further safety and efficacy testing will be required.*

RE-VERSE AD™ is an ongoing, global Phase III patient study initiated by Boehringer Ingelheim in 2014 to investigate idarucizumab* in the emergency setting.[34] This study involves dabigatran-treated patients who require emergency surgery or an invasive procedure or experience uncontrolled or life-threatening bleeding complications.[7] The study is designed to evaluate the types of patients and real-world situations that healthcare professionals may see in the emergency setting.[7] Broad inclusion criteria ensure that even severely ill or injured dabigatran-treated patients (e.g. patients with sepsis, a severe intracranial haemorrhage or a large vessel injury) who require urgent anticoagulant reversal may be enrolled.[7]

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