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Darexaban (YM150) prevents venous thromboembolism in Japanese patients undergoing major abdominal surgery: Phase III randomized, mechanical prophylaxis-controlled, open-label study

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ABSTRACT

Introduction: Darexaban (YM150) is an oral direct factor Xa inhibitor in clinical development for prophylaxis of venous thromboembolism (VTE) after major orthopaedic surgery. The objective of this study was to assess the efficacy and safety of darexaban 15 mg twice daily (bid) in Japanese patients undergoing major abdominal surgery.

Materials and Methods: In a Phase III, multicentre, randomized, open-label, mechanical prophylaxis-controlled, parallel-group study, adult patients (aged ≥40 years) were randomized to darexaban 15 mg bid or mechanical prophylaxis, for 28 days. The primary efficacy outcome was incidence of total VTE at Day 12. Adverse events (AEs) and bleeding events were recorded throughout the study.

Results: The total VTE incidence at Day 12 was 2.6% in the darexaban 15 mg bid group (95% confidence interval [CI]: 0.32, 9.07), compared with 15.0% (95% CI: 5.71, 29.84) in the mechanical prophylaxis group. During the investigational period, the incidence of all bleeding events was 9.5% in the darexaban 15 mg bid group and 3.9% in the mechanical prophylaxis group. In the darexaban 15 mg bid group, one patient experienced major bleeding and five patients experienced clinically relevant non-major (CRNM) bleeding. No patients in the mechanical prophylaxis group experienced major and/or CRNM bleeding. AEs were reported in 71.4% of patients in the darexaban 15 mg bid group and 76.5% of patients in the mechanical prophylaxis group; the most frequent AEs across both treatment groups were constipation and insomnia. No patients died during the study.

Conclusions: Based on these findings, darexaban is expected to be effective for the prevention of VTE in patients undergoing major abdominal surgery.

(Clinical trial registration number: NCT00942435)

Introduction

Venous thromboembolism (VTE) is a frequent complication of major abdominal surgery. In North America, symptomatic VTE is estimated to occur in around 3% of patients undergoing abdominal surgery in the absence of thromboprophylaxis [1]. In European patients undergoing abdominal surgery for cancer, the rate of VTE is approximately 12% without thromboprophylaxis [2]. In recent years, the incidence of VTE in Japan has been steadily on the increase [3], with recent studies reporting an incidence of VTE in the Japanese population following surgery comparable to that in western countries [4,5]. Results from a prospective, multicentre, epidemiological study in Japanese patients undergoing major abdominal surgery without thromboprophylaxis, reported a VTE incidence of 24.3%, with the majority of cases accounted for by distal deep vein thrombosis (DVT; 20.8%) [4]. Likewise, in a multicentre, open-label, randomized study in Japanese patients undergoing curative abdominal or pelvic surgery for cancer, VTE was observed in 19.4% of patients (all distal DVT) receiving only intermittent pneumatic compression (IPC) as thromboprophylaxis [6]. The reasons for this increased frequency of VTE in Japan remains to be fully elucidated, although the westernization of Japanese dietary habits and/or lifestyle [7,8] and the fact that more extensive surgeries are now performed, especially for abdominal malignancy care [9–11], are possible explanations.

Current Japanese guidelines for the prevention of VTE recommend stratification of patients into different risk categories according to the association of specific types of surgery with VTE, in addition to their individual risk factors [3,12,13]. For patients considered to be at a high risk of VTE (e.g. those aged ≥40 years old and undergoing major surgery for cancer), these guidelines recommend either IPC or anticoagulant

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therapy. In patients at the highest risk of VTE (e.g. those undergoing major surgery and with a past history of VTE), concomitant use of IPC or elastic compression stockings and anticoagulation therapy is recommended. Approved anticoagulant therapies for patients undergoing abdominal surgery in Japan are the low-molecular-weight heparin (LMWH) enoxaparin and the indirect factor Xa (FXa) inhibitor fondaparinux. However, data on their use in Japanese patients undergoing abdominal surgery is currently limited [6,14]. Moreover, these agents require parenteral administration, making them inconvenient for patients and costly for long-term use [15]. As such, the development of oral anticoagulants would be of immense value.

Over the past decade, FXa has emerged as an attractive target for novel anticoagulants due to its key position in the coagulation cascade and its limited roles outside of coagulation [16]. Consequently, inhibition of FXa has been targeted as a rational approach to anticoagulant therapy, with both direct and indirect inhibitors now available for the treatment of a range of indications [17–19]. One such direct, oral, FXa inhibitor is darexaban (YM150). Results from three studies in Caucasian patients undergoing elective orthopaedic surgery have demonstrated that darexaban is an effective antithrombotic agent for VTE prophylaxis [20–22]. Current Japanese VTE prevention guidelines recommend that patients (aged ≥40 years old) undergoing major general or urological surgery for cancer or gynaecological radical surgery for pelvic malignancy, receive the same prevention of VTE as for patients undergoing total hip or knee replacement [23]. Therefore, the primary objective of the present study was to assess the efficacy and safety of darexaban for prevention of VTE, when administered orally at a dose of 15 mg twice daily (bid), in Japanese patients undergoing major abdominal surgery.

Methods

Patients

Adult male and female patients (aged ≥40 years) scheduled to undergo major abdominal surgery (open laparotomy or laparoscopic surgery performed in the region between the diaphragm and pelvic floor, lasting for at least 45 minutes and conducted under general anaesthesia) and major general or urological surgery for cancer, or gynaecological radical surgery for pelvic malignancy were enrolled in this study. Patients undergoing other types of surgery, and who were considered to demonstrate additional risk factors for VTE, were also considered for inclusion. Major exclusion criteria were pre-existing or a history of symptomatic DVT or pulmonary embolism (PE); expected confinement to bed for at least 7 days prior to surgery; demonstrated haemorrhagic or coagulation disorders, or thrombocytopenia; concomitant use of antiplatelet or anticoagulant therapy, or planned treatment during the period from 1 week prior to surgery until the final study evaluation; history of major trauma, major surgery, or eye, spinal cord or brain surgery within 90 days prior to surgery, or such surgeries scheduled during the study period; clinically significant bleeding within 90 days of the planned surgical procedure; use of an intrathecal or epidural catheter that could not be removed 2 hours prior to the start of treatment; demonstrated uncontrolled, moderate or severe hypertension (systolic and/or diastolic blood pressure ≥160 mmHg and ≥100 mmHg, respectively); a gastrointestinal ulcer, myocardial infarction or stroke within 180 days of the planned surgical procedure; weight <40 kg at screening; demonstrated acute bacterial endocarditis; demonstrated retinopathy; demonstrated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) values >2 times the upper limit of normal (ULN) range or total bilirubin value >1.5 times ULN at screening; demonstrated ALT and/or AST values >3 times ULN, or total bilirubin value >2 times ULN at the post-operative examinations prior to randomization; and serum creatinine >1.5 times ULN at screening; serum creatinine increase of 25% from the screening visit to the post-operative examinations prior to randomization. Patients unsuitable for mechanical prophylaxis and patients for whom use of iodinated contrast media is contraindicated, were also excluded from the study, as were pre-menopausal women of childbearing potential who were not taking adequate contraception, or who were planning on becoming pregnant, were breastfeeding or were ≤2 years post-menopausal with positive results for serological pregnancy test (human chorionic gonadotropin) at screening.

Study Design

This was a Phase III multicentre, randomized, open-label, mechanical prophylaxis-controlled, parallel-group study conducted in Japan. The study was designed to examine the efficacy and safety of darexaban, based on the incidence of VTE after 28-day treatment with darexaban 15 mg bid, in patients undergoing major abdominal surgery. Since previous studies have demonstrated that long-term prophylaxis (25–31 days) is more effective than short-term prophylaxis (6–10 days) in patients at high risk of VTE [2,24], patients undergoing major abdominal surgery were randomized by a central registration/randomization system to darexaban 15 mg bid or mechanical prophylaxis on Day 1, for a total of 28 days (Fig. 1). Treatment allocation was hidden prior to randomization. In the mechanical prophylaxis group, patients received interventions according to standard practice at each study centre. The first dose of darexaban was administered (as one 15 mg tablet), or the first mechanical prophylaxis session was performed, within 3 days of surgery (designated as Day 1; Fig. 1). All subsequent doses of darexaban were administered as one 15 mg tablet bid, usually in the morning and evening, with at least 6 hours between doses. Follow-up observation was performed between 3 and 5 weeks after the final evaluation.

During the period from 1 week prior to abdominal surgery until the final study evaluation, patients were not permitted to take the following drugs: heparin, unfractionated heparin, LMWHs, aspirin, vitamin K antagonists, fondaparinux, thrombin inhibitors, thrombolytics, antiplatelet agents, dextran products and non-steroidal anti-inflammatory drugs (NSAIDs) (with the exception of selective cyclo-oxygenase-2 inhibitors and short-acting NSAIDs [$t_{1/2}$<12 hours]). For patients receiving darexaban, the concomitant use of any non-pharmacological therapy for VTE prophylaxis was not permitted during the period from randomization until the final study evaluation. However, the use of mechanical prophylaxis was permitted to prevent peri-operative VTE during the period between completion of surgery and the time that the patient could tolerate oral administration of drugs and was allocated to either of the treatment groups.

All patients were required to provide written informed consent prior to the observations and examinations performed during the observation period prior to the administration of study medication. The study (clinical trial registration number: NCT00942435) was reviewed and approved by the Institutional Review Board and Independent Ethics Committee and was conducted in accordance with the ethical principles set out in the Declaration of Helsinki, the applicable Good Clinical Practice guidelines, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines and all applicable local laws and regulations.

Assessments

During the screening visit (which could be from 28 days to 1 day prior to surgery), patients underwent measurement of weight, height, vital signs, 12-lead electrocardiogram (ECG), laboratory tests (blood biochemistry, urinalysis and cardiac markers [Troponin-T and creatine kinase–myocardial band]) and prothrombin time – International Normalized Ratio (PT-INR), together with a detailed medical history. Laboratory tests for hepatic and renal function were performed following surgery and prior to randomization. On Day 1 (randomization), vital signs were evaluated prior to the first dose of darexaban or first session of mechanical prophylaxis. Evaluations of vital signs,