Authorised medicines and regulatory considerations by EMA

Workshop - Challenges in drug development, regulation and clinical practice in immune thrombocytopenia

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Primary immune thrombocytopenia (ITP)

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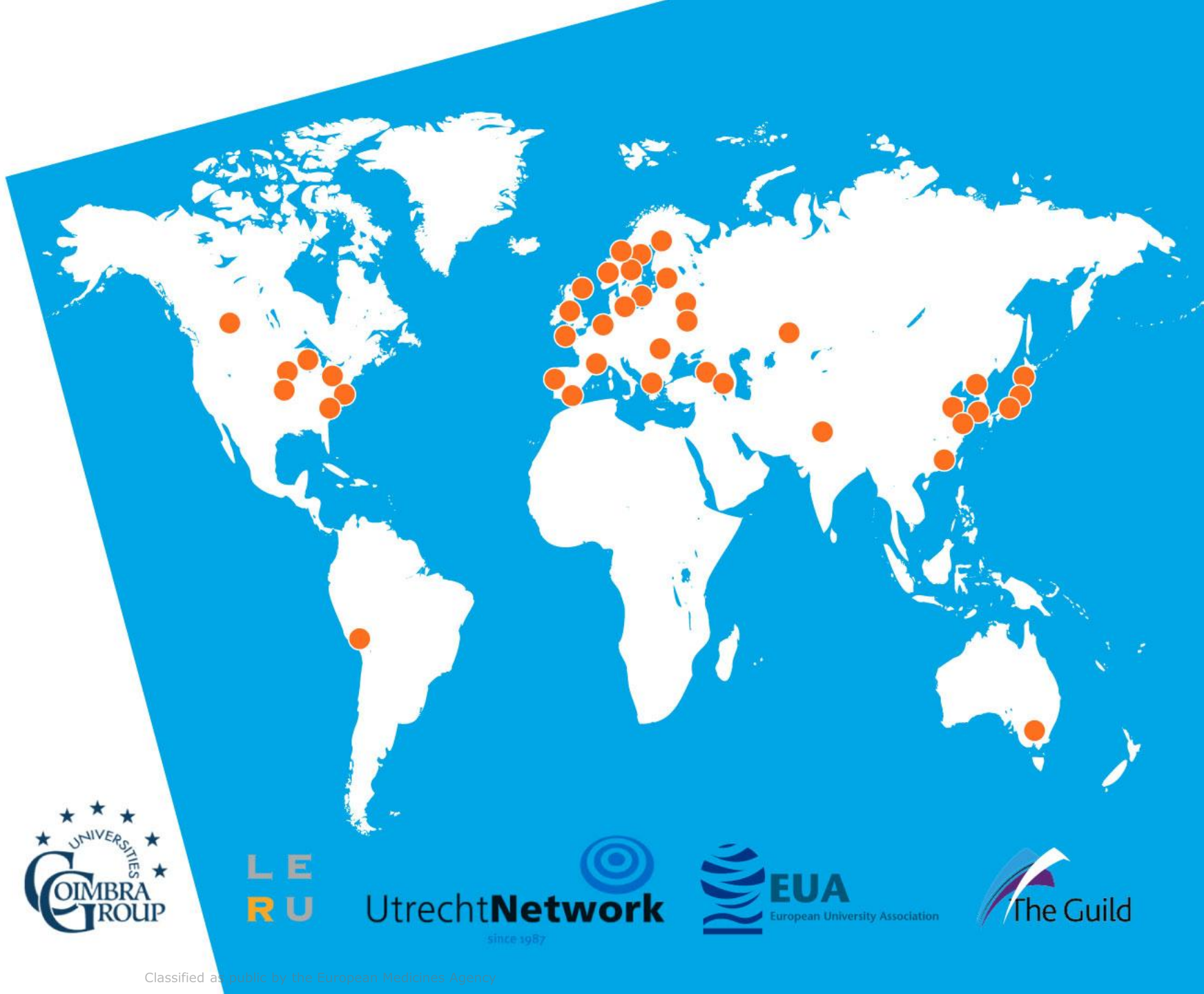
Thrombopoietin (TPO) receptor mimetics—also known as TPO receptor agonists (TPO-RAs)



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Nplate - Romiplostim

Therapeutic indications:

Adults:

Nplate is indicated for the treatment of primary immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

Paediatrics:

Nplate is indicated for the treatment of chronic primary immune thrombocytopenia (ITP) in paediatric patients one year of age and older who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

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Nplate – SmPC 4.2

4.2 Posology and method of administration

A subject's actual body weight at initiation of therapy should be used to calculate dose. **The once weekly dose of romiplostim should be increased by increments of 1 mcg/kg until the patient achieves a platelet count ≥ 50 x 109/L. Platelet counts should be assessed weekly until a stable platelet count (≥ 50 x 109/L for at least 4 weeks without dose adjustment) has been achieved.** Platelet counts should be assessed monthly thereafter and appropriate dose adjustments made as per the dose adjustment table (table 2) in order to maintain platelet counts within the recommended range. See table 2 below for dose adjustment and monitoring. A maximum once weekly dose of 10 mcg/kg should not be exceeded.

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Nplate – SmPC 5.1

5.1 Pharmacodynamic properties

Adults - The safety and efficacy of romiplostim was evaluated in two placebo-controlled, double-blind studies in adults with ITP who had completed at least one treatment prior to study entry and are representative of the entire spectrum of such ITP patients. Study S1 (20030212) evaluated patients who were non-splenectomised and had an inadequate response or were intolerant to prior therapies. Study S2 (20030105) evaluated patients who were splenectomised and continued to have thrombocytopenia. A significantly higher proportion of patients receiving romiplostim achieved a durable platelet response compared to patients receiving placebo in both studies**. Following the first 4-weeks of study romiplostim maintained platelet counts ≥ 50 x 109/L in between 50% to 70% of patients during the 6 months treatment period in the placebo-controlled studies.** Study S3 (20080435) was a single arm, open label study in adult patients who had an **insufficient response (platelet count ≤ 30 x 109/L) to first line therapy.**

Paediatrics - The safety and efficacy of romiplostim was evaluated in **two placebo-controlled, double-blind studies. Study S5 (20080279) was a phase 3 study with 24 weeks of romiplostim treatment and study S6 (20060195) was a phase 1/2 study with 12 weeks of romiplostim** treatment (up to 16 weeks for eligible responders who enter a 4-week pharmacokinetic assessment period). Both studies enrolled paediatric subjects (≥ 1 year to < 18 years of age) with thrombocytopenia (defined by a mean of 2 platelet counts ≤ 30 x 109/L with neither count > 35 x 109/L in both studies) with ITP, regardless of splenectomy status.

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Revolade - Eltrombopag

Therapeutic indications:

For the treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

For the treatment of paediatric patients aged 1 year and above with primary immune thrombocytopenia (ITP) lasting 6 months or longer from diagnosis and who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

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Revolade – SmPC 4.2 and 5.1

4.2 The lowest dose of eltrombopag to achieve and maintain a **platelet count ≥50 000/µl** should be used. Dose adjustments are based upon the platelet count response. Eltrombopag **must not be used to normalise platelet counts**. In clinical studies, platelet counts generally increased within 1 to 2 weeks after starting eltrombopag and decreased within 1 to 2 weeks after discontinuation.

5.1 Two phase III, randomised, double-blind, placebo-controlled studies RAISE (TRA102537) and TRA100773B and two open-label studies REPEAT (TRA108057) and EXTEND (TRA105325) evaluated the safety and efficacy of eltrombopag in adult patients with previously treated ITP. Overall, eltrombopag was administered to 277 ITP patients for at least 6 months and 202 patients for at least 1 year. In both RAISE and TRA100773B the response to eltrombopag relative to placebo was similar irrespective of ITP medicinal product use, splenectomy status and baseline platelet count (≤15 000/µl, >15 000/µl) at randomisation. **Response rate 54-59%.**

The safety and efficacy of eltrombopag in paediatric patients have been investigated in two studies TRA108062 (PETIT) and TRA115450 (PETIT2). Sustained response was seen in 50% of the initial responders during 20 out of 24 weeks in the PETIT 2 study and 15 out of 24 weeks in the PETIT study.

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Eltrombopag Viatris

Therapeutic indications:

For the treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

For the treatment of paediatric patients aged 1 year and above with primary immune thrombocytopenia (ITP) lasting 6 months or longer from diagnosis and who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

The main study - open label, randomised, single dose, 2-period, 2-sequence, crossover bioequivalence study comparing two 75 mg eltrombopag film-coated tablet formulations in 56 healthy subjects under fasting conditions.

https://www.ema.europa.eu/en/documents/assessment-report/eltrombopag-viatris-epar-public-assessment-report_en.pdf

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Eltrombopag Accord

Therapeutic indications:

For the treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

For the treatment of paediatric patients aged 1 year and above with primary immune thrombocytopenia (ITP) lasting 6 months or longer from diagnosis and who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

The main study - open label, balanced, randomized, two treatment (Test (T) and Reference (R)), two-sequence, two-period, single-dose, crossover bioequivalence study in 64 healthy adult, human male & female subjects under fasting conditions.

https://www.ema.europa.eu/en/documents/assessment-report/eltrombopag-accord-epar-public-assessment-report_en.pdf

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Eltrombopag Viatris – SmPC 4.2 and 5.1
Eltrombopag Accord – SmPC 4.2 and 5.1

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The safety and efficacy of eltrombopag in paediatric patients have been investigated in two studiesTRA108062 (PETIT) and TRA115450 (PETIT2). Sustained response was seen in 50% of the initial responders during 20 out of 24 weeks in the PETIT 2 study and 15 out of 24 weeks in the PETIT study.

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Doptelet - Avatrombopag

Therapeutic indications:

For the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

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Doptelet – SmPC 4.2 and 5.1

4.2 Use the lowest dose of Doptelet needed to achieve and maintain a **platelet count ≥ 50 × 109/L** as necessary to reduce the risk for bleeding. **Do not use avatrombopag to normalise platelet counts.** In clinical trials, platelet counts generally increased within 1 week after starting avatrombopag and decreased within 1 to 2 weeks after discontinuation. **The recommended starting dose of Doptelet is 20 mg (1 tablet) once daily with food. After initiating therapy, assess platelet counts at least once weekly until a stable platelet count ≥ 50 × 109/L and ≤ 150 × 109/L has been achieved.** Twice weekly platelet count monitoring should be conducted during the first weeks of therapy in patients receiving avatrombopag only once or twice weekly. Due to the potential risk of platelet counts above 400 × 109/L within the first weeks of treatment patients should be carefully monitored for any signs or symptoms of thrombocytosis.

5.1 The efficacy of Doptelet in adult patients with chronic immune thrombocytopenia was evaluated in a Phase 3, multicentre, randomised, double-blind, placebo-controlled trial (Study 302). Patients had previously received one or more prior chronic immune thrombocytopenia therapies and had an average of screening and baseline platelet counts < 30 × 109/L. Patients were centrally stratified by splenectomy status, baseline platelet count (≤ 15 or > 15 × 109/L), and use of concomitant chronic immune thrombocytopenia medicinal products, and then. Patients received a starting dose of 20 mg once daily, with doses subsequently titrated based **randomised (2:1) to receive either avatrombopag or placebo for 6 months**on platelet response. **Avatrombopag-treated patients had a longer duration of platelet counts ≥ 50 × 109/L in the absence of rescue therapy than those who received placebo (median 12.4 [0, 25] vs 0 [0, 2] weeks, respectively, p < 0.0001).**

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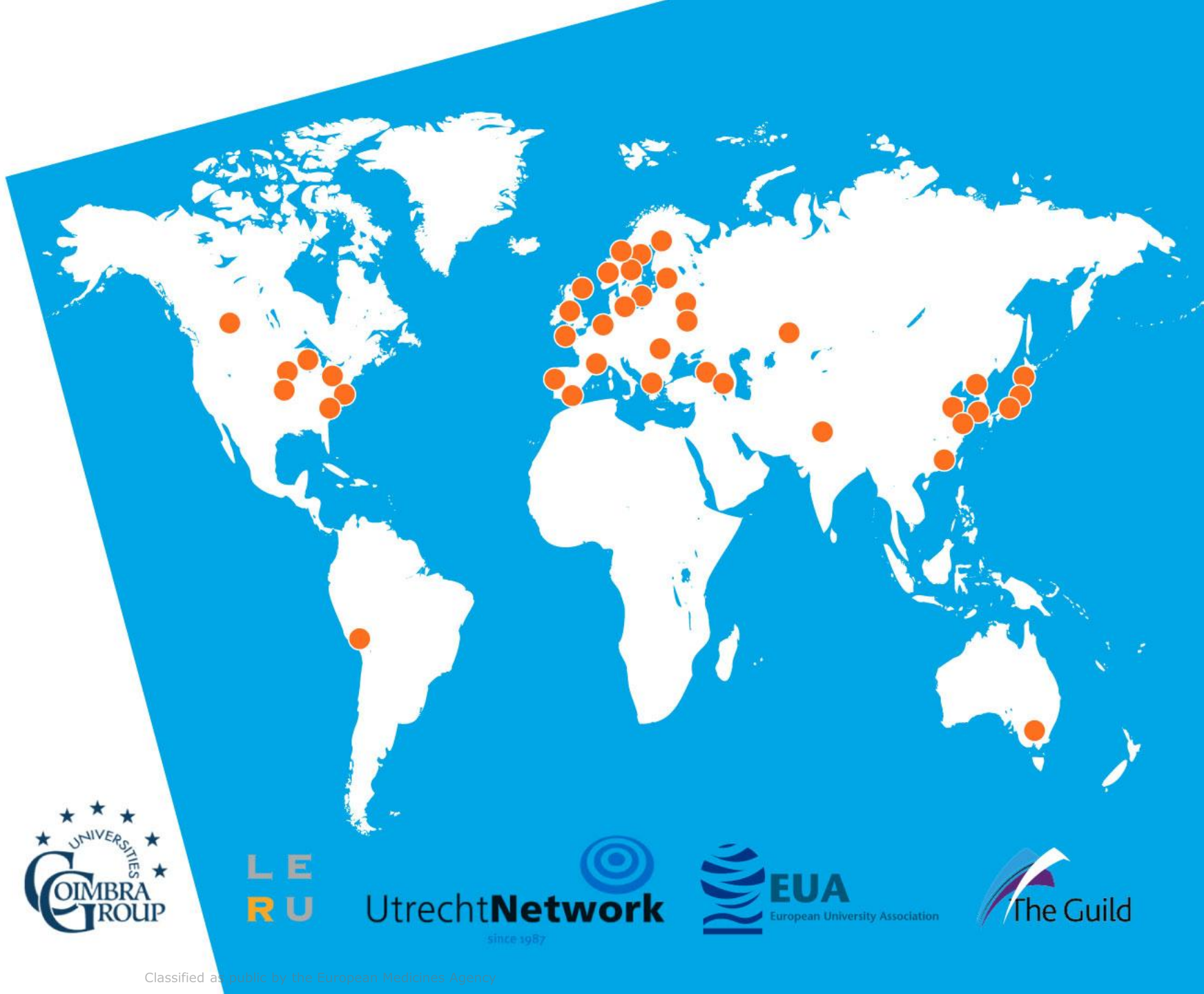
Spleen tyrosine kinase (SYK) inhibition



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Tavlesse - Fostamatinib

Therapeutic indications:

For the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (see section 5.1).

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Tavlesse – SmPC 4.2 and 5.1

4.2 Fostamatinib dosing requirements must be individualised based on the patient's platelet counts. **The lowest dose of fostamatinib to achieve and maintain a platelet count of at least 50 000/µL should be used**. Dose adjustments are based upon the platelet count response and tolerability (see table 2). The recommended starting dose of fostamatinib is 100 mg twice daily. After initiating fostamatinib, the dose can be increased to 150 mg twice daily after 4 weeks based on platelet count and tolerability. A daily dose of 300 mg daily must not be exceeded. Fostamatinib dose modification is recommended based on tolerability and platelet counts. Management of some adverse reactions may require dose interruption, reduction, or discontinuation (see table 1 and table 2).

5.1 The efficacy and safety of fostamatinib has been demonstrated **in two Phase III, randomised, doubleblind, placebo-controlled studies** (C788-047 and C788-048) in adult patients with **previously treated** persistent (3-12 months since diagnosis) or chronic (greater than 12 months since diagnosis) ITP. Randomised, placebo-controlled studies A total of 150 patients with persistent or chronic ITP, who had an insufficient response to previous treatment (which included corticosteroids, immunoglobulins, splenectomy, and/or a thrombopoietin receptor agonists) were enrolled in two identical, double-blind, placebo-controlled studies that were conducted in different countries. For each study, patients were **randomised 2:1 to fostamatinib or placebo for 24 weeks**. The efficacy of fostamatinib was based on the primary endpoint of stable platelet response (at least 50 000/µL on at least 4 of the 6 visits between Weeks 14 to 24). **An initial therapeutic response (platelet count ≥ 50 000/µL) was observed within 6 weeks for most responders (11 of 17 responders) and within 12 weeks for all stable responders.**

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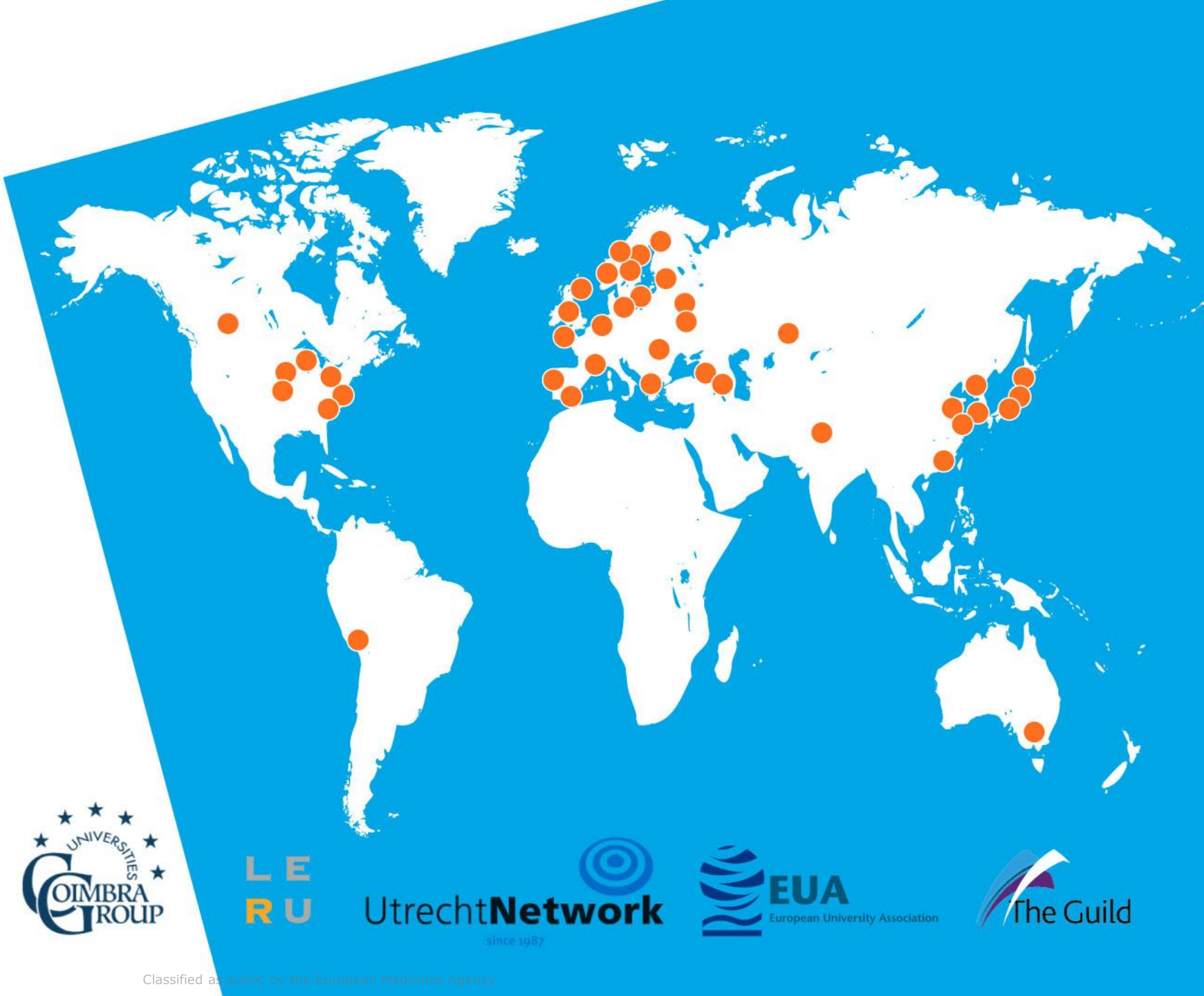
Bruton’s tyrosine kinase (BTK) inhibition



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Wayrilz - Rilzabrutinib

Therapeutic indications:

For the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (see section 5.1).

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Wayrilz – SmPC 4.2 and 5.1

4.2 The recommended dose of rilzabrutinib is 400 mg twice daily.

5.1 The safety and efficacy of rilzabrutinib in adult patients with primary persistent or chronic immune thrombocytopenia (ITP) was evaluated in **a Phase 3, randomized, double-blind (DB), placebocontrolled, parallel-group study** consisting of 24 weeks of blinded treatment, followed by an openlabel (OL) period of 28 weeks and long-term extension (LTE) period during both of which all patients received rilzabrutinib (LUNA 3 Study). The patients enrolled in this study did not have a sustained response to either intravenous immunoglobulin (IVIg/anti-D) or corticosteroid (CS), or had a documented intolerance or insufficient response to any appropriate course of standard-of-care ITP therapy. **The primary endpoint was durable platelet response. A durable platelet response was the achievement of a weekly platelet count ≥ 50 000/μL for at least 8 out of the last 12 weeks of the 24-week DB period in the absence of rescue therapy, The proportion of patients achieving durable response was significantly higher in the rilzabrutinib group (23.3%) compared to the placebo group (0%) during the DB period.**

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