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A Phase III Clinical Trial Program Investigating the Efficacy and Safety of Ianalumab in Patients with Primary Immune Thrombocytopenia (VAYHIT1 and VAYHIT2) and Warm Autoimmune Hemolytic Anemia (VAYHIA)

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Background: Immune thrombocytopenia (ITP) and warm autoimmune hemolytic anemia (wAIHA) are characterized by autoantibody destruction of platelets and red blood cells, respectively. Autoreactive B cells play a role in the pathophysiology of ITP and wAIHA. Serum levels of B-cell activating factor (BAFF) are elevated in these disorders and correlate with increased disease activity. Ianalumab is a novel, fully human immunoglobulin G1 monoclonal antibody that targets BAFF receptor (BAFF-R) and has a unique dual mechanism of action: direct antibody-dependent cellular cytotoxicity-mediated B-cell depletion and inhibition of B-cell differentiation, proliferation and survival via blockade of BAFF-R-mediated signaling. Corticosteroids (CS) are the standard first-line treatment for ITP; however, few patients achieve a long-term response. Additionally, extended and recurrent use of CS is associated with substantial toxicity. Thrombopoietin receptor agonists (TPO-RAs), such as eltrombopag, are commonly used second-line ITP treatments and often achieve a response; however, responses are rarely maintained once treatment ends, so chronic administration is typically required. For wAIHA, few treatments have been approved, and patients rarely achieve durable responses on CS or off-label rituximab. Thus, there are significant unmet needs for patients with ITP or wAIHA.

Aim: We report the designs of the randomized, double-blind, multicenter, 3-arm Phase III VAYHIT1 (NCT05653349), VAYHIT2 (NCT05653219) and VAYHIA (NCT05648968) trials. The trials aim to assess whether ianalumab, working with a distinct and complementary mechanism to standard-of-care treatments, can induce durable responses in patients with ITP or wAIHA.

Trial designs:

VAYHIT1 and **VAYHIT2** will assess the efficacy and safety of ianalumab vs placebo in addition to first-line CS and short-term eltrombopag, respectively, in adults with primary ITP. In both trials, patients will be randomized 1:1:1 to intravenous (IV) low-dose ianalumab, high-dose ianalumab or placebo every 4 weeks (wks). The primary endpoint in both trials is the time from randomization to treatment failure, defined as platelet count <30 G/L later than 8 wks from randomization, need for rescue treatment later than 8 wks from randomization, start of a new ITP therapy, or death. In VAYHIT2, ineligibility to taper or inability to discontinue eltrombopag after the completion of treatment with ianalumab or placebo will also be assessed as treatment failure. Secondary endpoints include response rate, complete response rate and safety (**Table**).

VAYHIA will assess the efficacy and safety of ianalumab vs placebo in adults with wAIHA who have failed ≥1 treatment. Patients will be randomized 1:1:1 to IV low-dose ianalumab, high-dose ianalumab or placebo every 4 wks. Selected supportive care is allowed. The primary endpoint is durable hemoglobin (Hb) response, defined as Hb ≥10 g/dL and an Hb increase of ≥2 g/dL from baseline for ≥8 consecutive wks between Wk 9 and Wk 25 in the absence of rescue or prohibited treatment. The key secondary endpoint is duration of durable Hb response (**Table**). An optional open-label crossover period will allow patients who receive placebo and do not achieve a durable Hb response to receive high-dose ianalumab.
Patients from all 3 trials will be monitored for efficacy until treatment failure (or up to 39 months after the last patient was randomized, whichever comes first) and safety for up to 2 years.
Conclusions: These trials have been designed based on the hypothesis that, when administered early in disease progression, medical therapy targeting complementary physiological pathways may restore self-tolerance in patients with ITP and wAIHA. Ianalumab in combination with standard of care is expected to safely induce a high response rate that will be maintained beyond treatment completion. Ianalumab may address the unmet needs for patients with ITP and wAIHA.
Current status: At the time of writing, VAYHIT1, VAYHIT2 and VAYHIA are recruiting. The open-label, single-arm, Phase II VAYHIT3 trial is also assessing ianalumab in patients with primary ITP previously treated with at least 1 CS and 1 TPO-RA (NCT05885555).

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OffLabel Disclosure: Off-label use of rituximab is mentioned in the Background section, to explain that it is sometimes used off-label in patients with wAIHA.

Table. VAYHIT1, VAYHIT2 and VAYHIA study design

Study characteristic	VAYHIT1	VAYHIT2	VAYHIA
Patient population	• Adults with primary ITP who responded to first-line CS treatment prior to randomization	• Adults with primary ITP who had an insufficient response to, or relapsed after, first-line treatment with CS (+/− IVIg)	• Adults with primary or certain secondary wAIHA who failed ≥1 previous treatment
Key inclusion criteria	• Aged ≥18 years • Platelet count <30 G/L • Responded (platelet count ≥50 G/L) to CS (+/− IVIg) at any time prior to randomization	• Aged ≥18 years • Platelet count <30 G/L • Assessed need for second-line treatment • Eligible to receive eltrombopag	• Aged ≥18 years • Hb >10 g/dL with anemia-related symptoms • Primary or secondary wAIHA with an insufficient response to, or relapse after, ≥1 treatments
Key exclusion criteria	• Previous receipt of ITP treatment (except for CS and/or IVIg up to 28 days before randomization) • Previous use of B-cell depleting therapy (eg rituximab)	• Previous receipt of second-line ITP treatment (except for CS therapy +/− IVIg) • Previous use of B-cell depleting therapy (eg rituximab)	• wAIHA secondary to hematologic disease involving bone marrow • Use of B-cell depleting therapy (eg rituximab) <12 wks prior to randomization
Randomization	• Approximately 225 patients will be randomized in a 1:1:1 ratio • Stratified by CS treatment (prednis[o]lone or dexamethasone)	• Approximately 150 patients will be randomized in a 1:1:1 ratio • Stratified by time since diagnosis	• Approximately 90 patients will be randomized in a 1:1:1 ratio • Stratified by prior rituximab exposure
Treatment administration	• Low-dose ianalumab, high-dose ianalumab or placebo will be administered intravenously every 4 wks • CS will be administered as per the standard-of-care regimen selected prior to randomization	• Low-dose ianalumab, high-dose ianalumab or placebo will be administered intravenously every 4 wks • Eltrombopag will be administered orally to all patients once daily and tapered after the double-blinded treatment period in patients with stable platelet counts ≥50 G/L	• Lower-dose ianalumab, higher-dose ianalumab or placebo will be administered intravenously every 4 wks • Limited supportive care is allowed
Primary endpoint	• Time from randomization to treatment failure, defined as the first of: – Platelet count <30 G/L later than 8 wks from randomization – Need for a rescue treatment* later than 8 wks from randomization – Start of second-line ITP treatment – Death	• Time from randomization to treatment failure, defined as the first of: – Platelet count <30 G/L – Need for a rescue treatment* later than 8 wks from randomization – Start of new ITP treatment – Ineligibility to taper or inability to continue eltrombopag – Death	• Durable Hb response defined as Hb ≥10 g/dL and an Hb increase of ≥2 g/dL from baseline for ≥8 consecutive wks between Wk 9 and Wk 25 in the absence of rescue[§] or prohibited treatment
Secondary endpoints	• Response rate,[†] complete response rate[‡] and duration of complete response • Time from randomization to complete response • Use of rescue treatment* • Frequency and severity of bleeding events • Frequency of AEs and severe infections • Change from baseline in patient-reported quality of life measures	• Response rate,[†] complete response rate,[‡] best response rate, duration of response and complete response • Time from randomization to response and complete response • Probability to be free from treatment failure at end of planned treatment period • Use of rescue treatment* • Frequency and severity of bleeding events • Frequency of AEs and severe infections • Change from baseline in patient-reported quality of life measures	• Duration of Hb response[¶§] • Response rate,** complete response rate[††] and Hb level • Time from randomization to first durable response, response and complete response • Use of rescue treatment[§] • Frequency of AEs • Change from baseline in patient-reported quality of life measures

*Any treatment for ITP given to rapidly increase platelet count (eg CS, IVIg or platelet transfusion); †Defined as proportion of patients with any platelet count ≥50 G/L in the absence of rescue treatment or new ITP treatment; ‡Defined as proportion of patients with any platelet count ≥100 G/L in the absence of rescue treatment or new ITP treatment; §Any additional wAIHA-directed treatment, which is not considered prohibited medication, or an increase in the dosage of supportive care by >20% compared with pre-enrollment dose; ¶Key secondary endpoint; ‖Defined as time from first Hb assessment showing durable response to the earliest of the following events: Hb <10 g/dL for ≥2 consecutive weekly assessments, the start of any rescue or prohibited treatment, or death; **Defined as proportion of patients with Hb level ≥10 g/dL and ≥2 g/dL increase from baseline, or normalization of Hb (Hb level ≥11 g/dL [women] or ≥12 g/dL [men]) without biochemical resolution of hemolysis; ††Defined as proportion of patients achieving normalization of Hb (Hb level ≥11 g/dL [women] or ≥12 g/dL [men]) with no evidence of hemolysis and absence of red blood cell transfusions
AE, adverse event; CS, corticosteroid; Hb, hemoglobin; ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; wAIHA, warm autoimmune hemolytic anemia; wk, week

Figure 1

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