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## MEDIA & INVESTOR RELEASE

# Novartis investigational oral therapy iptacopan (LNP023) shows benefit as monotherapy in treatment-naïve patients with rare and life-threatening blood disorder paroxysmal nocturnal hemoglobinuria

- *First-in-class, oral, targeted factor B inhibitor iptacopan substantially reduced both intra- and extravascular hemolysis when given as monotherapy in a Phase II study of anti-C5 naïve paroxysmal nocturnal hemoglobinuria (PNH) patients*[1]

- *New results are promising for potential use of iptacopan as monotherapy in PNH, a rare and life-threatening blood disorder*[2,3]*; results from a previous Phase II study showed iptacopan substantially improved hematological response as add-on to standard-of-care (eculizumab)*[4]

- *The FDA has granted Breakthrough Therapy Designation to iptacopan for PNH*[5]*; it also has received orphan drug designation for PNH from both the FDA and EMA*[6]

- *Iptacopan is also in development for several rare renal conditions with complement system (part of the innate immune system) involvement, targeting a key driver of these diseases*[7,8]

- *Recently presented Phase II data showed iptacopan reduced proteinuria and stabilized kidney function in IgA nephropathy (IgAN)*[9]*, and improved estimated glomerular filtration rate (eGFR) slope and stabilized kidney function in C3 glomerulopathy (C3G)*[10]

**Basel, June 11, 2021** — Novartis today announced new Phase II data for iptacopan (LNP023), an investigational oral treatment for paroxysmal nocturnal hemoglobinuria (PNH), presented at the 26th Annual Congress of the European Hematology Association (EHA). In the study (NCT03896152), treatment with 12 weeks of iptacopan monotherapy was generally well tolerated with no unexpected safety findings and resulted in rapid and durable transfusion-free improvement of hemoglobin levels in the majority of patients[1].

“Currently, 20-50% of PNH patients treated with standard-of-care anti-C5 therapies remain transfusion-dependent due to persistent extravascular hemolysis, and an additional 20-40% exhibit varying degrees of residual anemia,” said lead author Professor Jun Ho Jang, Division of Hematology-Oncology, Sungkyunkwan University School of Medicine. “These results show that oral iptacopan blocks both intra- and extravascular hemolysis in patients with hemolytic PNH who have not previously been treated with an anti-C5. When considered with the

findings of the previous Phase II study, these data suggest that iptacopan may provide additional benefits beyond those seen with current standard-of-care therapies, and may potentially change the PNH treatment paradigm."

All patients completing at least 12 weeks of iptacopan treatment (n=11) achieved the primary endpoint of at least a 60% reduction in their lactate dehydrogenase (LDH) levels, a biomarker of intravascular hemolysis[1]. Importantly, with the exception of one patient receiving a single red blood cell (RBC) transfusion, all patients remained transfusion-free through 12 weeks of study[1]. Patients also showed improvement in other biomarkers of hemolysis and a marked increase in the proportion of PNH-type RBCs, indicating overall control of both intra- and extravascular hemolysis[1].

No serious adverse events or thromboembolic events were reported during the 12-week treatment period and the study yielded no unexpected safety results[1]. Two participants discontinued iptacopan treatment before completing 12 weeks of treatment: one due to a non-serious headache, the other by physician decision due to worsening of pre-existing neutropenia[1]. The most common adverse events were headache (31% of patients), abdominal discomfort (15%), blood alkaline phosphatase increase (15%), cough (15%), oropharyngeal pain (15%), pyrexia (raised body temperature; 15%), and upper respiratory infection (15%)[1].

"PNH is a rare and life-threatening blood disorder with often debilitating symptoms," said John Tsai, Head Global Drug Development and Chief Medical Officer, Novartis. "New treatment options are needed, and these positive results further strengthen the profile of iptacopan as a promising oral monotherapy. We are excited to continue to explore the potential of iptacopan as new standard-of-care treatment for PNH in the ongoing Phase III study."

PNH, which is characterized by complement-driven hemolysis, thrombosis and impaired bone marrow function[11,12], results in anemia, fatigue and other debilitating symptoms that can impact patients' quality of life[13-15]. Despite treatment with current anti-C5 standard-of-care therapies, a large proportion of PNH patients remain anemic and dependent on transfusions[2,3,11,13,15].

In results from the separate open-label Phase II study (NCT03439839), published in *The Lancet Haematology*, iptacopan improved hematological response and biomarkers of disease activity in PNH patients with active hemolysis despite treatment with the anti-C5 eculizumab[4]. This benefit was maintained in patients who stopped eculizumab treatment[4].

**About iptacopan**
Iptacopan is an investigational first-in-class, orally administered targeted factor B inhibitor of the alternative complement pathway[7,8]. It acts upstream of the C5 terminal pathway, preventing not only intravascular but also extravascular hemolysis in PNH[1]. In doing so, iptacopan may have a therapeutic advantage over current standard-of-care by targeting a key part of the biology responsible for PNH[7,8].

Discovered at the Novartis Institutes for BioMedical Research, iptacopan is currently in development for a number of complement-driven diseases where significant unmet needs exist, including IgAN, C3G, atypical hemolytic uremic syndrome (aHUS), and membranous nephropathy (MN), as well as the blood disorder PNH. Novartis has initiated a Phase III study of iptacopan as monotherapy in PNH.

Based on disease prevalence and the positive interim data from Phase II studies, iptacopan has received orphan drug designations from the FDA and EMA in C3G and PNH[6], FDA Breakthrough Therapy Designation in PNH[5], EMA PRIME designation for C3G[16], and EMA orphan drug designation in IgAN[17].

**About the Study**
NCT03896152 is a Phase II, multinational, multicenter, open-label, randomized, 2-cohort, dose-ranging trial to evaluate the efficacy, safety and pharmacokinetics/pharmacodynamics of

iptacopan monotherapy in adult PNH patients with active hemolysis and no complement inhibition in the prior 3 months[1]. The primary objective of the study was to assess the percentage of patients with 60% reduction in LDH or LDH below upper limit of normal (ULN) up to 12 weeks of treatment[1].

The study assessed four iptacopan doses in two separate cohorts with two sequential treatment periods each[1]. A total of 13 patients were randomized to receive either 25 mg iptacopan twice daily up to week four, rising to 100 mg iptacopan twice daily from weeks five to 12 (cohort 1; n=7), or 50 mg iptacopan twice daily up to week four, rising to 200 mg iptacopan twice daily from weeks five to 12 (cohort 2; n=6)[1]. Two participants discontinued iptacopan treatment before completing 12 weeks of treatment: one due to a non-serious headache, the other by physician decision due to worsening of pre-existing neutropenia[1].

After the 12-week main treatment period, patients responding to iptacopan treatment had the option to enter an approximately two-year treatment extension period[1].

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