Press Release

ASH: rilzabrutinib demonstrated significant patient benefit in the first positive phase 3 study of a BTK inhibitor in ITP

- Pivotal phase 3 data show rapid and durable platelet response, reduced bleeding and need for rescue response, and improved physical fatigue and quality of life measures in patients with persistent or chronic ITP
- Results underscore the safety and efficacy of rilzabrutinib and its potential as the first BTK inhibitor in ITP
- Rilzabrutinib is currently under regulatory review in the US and the EU

Paris, December 7, 2024. Positive results from the pivotal LUNA 3 phase 3 study of rilzabrutinib in adults with persistent or chronic immune thrombocytopenia (ITP), a rare immune-mediated disease, reinforce the efficacy and safety of rilzabrutinib, an oral, reversible, covalent Bruton's tyrosine kinase (BTK) inhibitor, and further support its potential as a first-in-class treatment for ITP. Platelet response was achieved in 65% (n=86) of patients receiving rilzabrutinib compared to 33% (n=23) of patients on placebo. The primary endpoint was met, with rilzabrutinib demonstrating durable platelet response in 23% of ITP adult patients compared to 0% on the placebo arm (p<0.0001), as well as key secondary endpoints including reduced bleeding, number of weeks with platelet response, the need for rescue therapy use, and improved physical fatigue and quality of life measures.

These results were presented today at the 66th American Society of Hematology (ASH) Annual Meeting and Exposition in San Diego, December 7-10, 2024.

> ***David Kuter, MD***
> Director of Clinical Hematology at Massachusetts General Hospital and Professor of Medicine at Harvard Medical School, study author
> *"People living with immune thrombocytopenia who cannot tolerate or do not respond to medications aimed at raising platelet counts are at risk of uncontrolled bleeding and often endure side effects from steroids and other available therapies. A significant percentage of these patients also suffer from severe fatigue and an impaired quality of life. I'm encouraged by the robust therapeutic effects I've seen in patients of the LUNA 3 study across all aspects of the disease, including clinically meaningful and sustained improvements in platelet count, quality of life metrics, reduction in bleeding, and a favorable safety profile."*

In the pivotal LUNA 3 study, adult patients with persistent or chronic ITP and severely low platelet counts (median of 15,000/µL) received oral rilzabrutinib 400 mg twice a day (n=133) or placebo (n=69) for up to 24 weeks followed by 28 weeks of open-label period and demonstrated the following results:

- Platelet response (defined as ≥50,000/µL or ≥30,000–<50,000/µL and doubled from baseline) was achieved in 65% (n=86) of patients receiving rilzabrutinib compared to 33% (n=23) of patients on placebo
- The primary endpoint of durable platelet response, defined as the proportion of participants able to achieve platelet counts at or above 50,000/µL for at least 8 out of the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy was met in 23% (n=31) of patients receiving rilzabrutinib compared to 0% of patients on placebo (p<0.0001)
- For the combined double-blind and open-label periods, durable response was achieved in 29% (n=38) of rilzabrutinib-randomized patients as of the data cutoff. Results of additional patients following data cutoff have not yet been analyzed
- Significant improvements were observed with rilzabrutinib vs. placebo in bleeding (based on the Immune Thrombocytopenic Purpura Bleeding Score), with a mean change (SE) from baseline at week 25 of –0.04 (0.02) vs 0.05 (0.02; p=0.0006)

- Patients on rilzabrutinib were approximately three times more likely to achieve a platelet response than patients on placebo (hazard ratio=3.1 [95% confidence interval, 1.9-4.9]; $p<0.0001$) and had a median time to first platelet response of 36 days vs. median not achieved by patients on placebo. Among responders on rilzabrutinib, median time to response was 15 days
- Rilzabrutinib significantly reduced the need for rescue therapy by 52% compared to placebo ($p=0.0007$)
- Significant and clinically meaningful improvements in physical fatigue (based on the Immune Thrombocytopenic Purpura Patient Assessment Questionnaire ITP-PAQ Item 10 score) were observed in patients on rilzabrutinib from baseline at week 13 with a least squares (LS) mean change of 8.0 vs. –0.1 for placebo (LS mean difference 8.1, $p=0.01$). The improvement of fatigue was sustained through week 25 and was also noted in non-durable platelet responders, along with improved outcomes in other quality-of-life domains

The safety profile of rilzabrutinib was consistent with previous studies. The rates of adverse events (AEs) were similar in patients receiving rilzabrutinib and patients receiving placebo; the most common treatment-related AEs for rilzabrutinib were mild/moderate (grade 1/2), including diarrhea (23%), nausea (17%), headache (8%) and abdominal pain (6%).

Rilzabrutinib is an investigational medicine, and its safety and efficacy have not been fully evaluated by any regulatory authority. Rilzabrutinib is currently under regulatory review in the US and the EU, with a US Food and Drug Administration target action date of August 29, 2025.

> ***Dietmar Berger, MD, PhD***
> Chief Medical Officer, Global Head of Development, Sanofi
> *"These new data support the potential of rilzabrutinib to provide robust and durable platelet response in immune thrombocytopenia, offering hope for patients with limited treatment options. Based on its ability to target BTK, an enzyme that plays a critical role in many types of immune cells, we believe rilzabrutinib also has the potential to improve patient outcomes in multiple rare blood and autoimmune disorders."*

In addition to ITP, rilzabrutinib is being studied across a variety of immune-mediated diseases. Positive results from a phase 2 study of rilzabrutinib in warm autoimmune hemolytic anemia (wAIHA) and preclinical data in sickle cell disease were also presented at ASH.

A full list of rilzabrutinib abstracts and presentations is included below.
5 abstracts; 1 oral presentation

Abstract title	**Presentation details**
Immune thrombocytopenia	
Abstract #5: Efficacy and safety of oral Bruton tyrosine kinase inhibitor (BTKi) rilzabrutinib in adults with previously treated immune thrombocytopenia (ITP): a phase 3, placebo-controlled, parallel-group, multicenter study (LUNA 3)	*Press briefing*: Saturday, December 7, 8:30 am PT *Oral presentation*: Sunday, December 8, 3:20 pm PT (Plenary Session)
Abstract #2552: Improved health-related quality of life (HRQoL) with oral Bruton tyrosine kinase inhibitor (BTKi) rilzabrutinib vs placebo in adults with previously treated immune thrombocytopenia (ITP): phase 3 LUNA 3 multicenter study	*Poster presentation*: Sunday, December 8, 6:00-8:00 pm PT
Abstract #3944: Clinical burden of illness in patients with persistent or chronic immune thrombocytopenia treated with advanced therapies in the United States	*Poster presentation*: Sunday, December 8, 6:00-8:00 pm PT
Warm autoimmune hemolytic anemia	
Abstract #3836: Part A efficacy and safety of oral Bruton tyrosine kinase inhibitor (BTKi) rilzabrutinib in patients with	*Poster presentation*: Monday, December 9, 6:00-8:00 pm PT

warm autoimmune hemolytic anemia (wAIHA): multicenter, open-label, phase 2b study	
Research	
Abstract #2482: Bruton tyrosine kinase inhibitor rilzabrutinib reduces vaso-occlusion and markers of inflammation and adhesion in transgenic mice with sickle cell disease	*Poster presentation*: Sunday, December 8, 6:00-8:00 pm PT

About the LUNA 3 study

LUNA 3 (NCT04562766) is a randomized, multicenter, phase 3 study evaluating the efficacy and safety of rilzabrutinib vs. placebo in adult and adolescent patients with persistent or chronic ITP. Patients received either oral rilzabrutinib 400 mg twice a day or placebo through a 12- to 24-week double-blind treatment period, followed by a 28-week open-label treatment, and then a 4-week safety follow-up or long-term extension period. The adolescent part of the study is ongoing. The primary endpoint is durable platelet response, defined as the proportion of participants able to achieve platelet counts at or above 50,000/µL for at least 8 out of the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy. Secondary endpoints include the number of weeks with and time to platelet responses, rescue therapy use, physical fatigue score, and bleeding score.

About rilzabrutinib

Rilzabrutinib is an oral, reversible, covalent BTK inhibitor that has the potential to be a first- and best-in-class treatment of several immune-mediated and inflammatory diseases. BTK, expressed in B cells, macrophages, and other immune cells, plays a critical role in inflammatory pathways and multiple immune-mediated disease processes. With the application of Sanofi's TAILORED COVALENCY® technology, rilzabrutinib can selectively inhibit the BTK target while potentially reducing the risk of off-target side effects.

Rilzabrutinib was granted fast track designation by the US Food and Drug Administration (FDA) for the treatment of ITP in November 2020 and was previously granted orphan drug designation.

Rilzabrutinib is being studied across a variety of immune-mediated diseases, including immune thrombocytopenia, warm autoimmune hemolytic anemia (phase 2), asthma (phase 2), chronic spontaneous urticaria (phase 2).

Rilzabrutinib is currently under clinical investigation, and its safety and efficacy have not been evaluated by any regulatory authority.

About ITP

ITP is a rare, complex autoimmune disorder characterized by low platelet counts (less than 100,000/µL) resulting from both increased platelet destruction and decreased platelet production. Beyond bruising and bleeding, which can include potentially life-threatening episodes like intracranial hemorrhage, people living with ITP may experience arterial or venous thrombosis. They also often experience easily overlooked symptoms that significantly impair their quality of life, such as unexplained fatigue, anxiety or depression, and cognitive impairment. With its multiple mechanisms of action that target B cells and macrophages, both of which express BTK and potentially other inflammatory pathways, rilzabrutinib may address the underlying mechanisms responsible for a wide range of ITP complications.

About Sanofi

We are an innovative global healthcare company, driven by one purpose: we chase the miracles of science to improve people's lives. Our team, across the world, is dedicated to transforming the practice of medicine by working to turn the impossible into the possible. We provide potentially life-changing treatment options and life-saving vaccine protection to millions of people globally, while putting sustainability and social responsibility at the center of our ambitions.
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Sanofi forward-looking statements
This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements are statements that are not historical facts. These statements include projections and estimates and their underlying assumptions, statements regarding plans, objectives, intentions, and expectations with respect to future financial results, events, operations, services, product development and potential, and statements regarding future performance. Forward-looking statements are generally identified by the words "expects", "anticipates", "believes", "intends", "estimates", "plans" and similar expressions. Although Sanofi's management believes that the expectations reflected in such forward-looking statements are reasonable, investors are cautioned that forward-looking information and statements are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of Sanofi, that could cause actual results and developments to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include among other things, the uncertainties inherent in research and development, future clinical data and analysis, including post marketing, decisions by regulatory authorities, such as the FDA or the EMA, regarding whether and when to approve any drug, device or biological application that may be filed for any such product candidates as well as their decisions regarding labelling and other matters that could affect the availability or commercial potential of such product candidates, the fact that product candidates if approved may not be commercially successful, the future approval and commercial success of therapeutic alternatives, Sanofi's ability to benefit from external growth opportunities, to complete related transactions and/or obtain regulatory clearances, risks associated with intellectual property and any related pending or future litigation and the ultimate outcome of such litigation, trends in exchange rates and prevailing interest rates, volatile economic and market conditions, cost containment initiatives and subsequent changes thereto, and the impact that pandemics or other global crises may have on us, our customers, suppliers, vendors, and other business partners, and the financial condition of any one of them, as well as on our employees and on the global economy as a whole. The risks and uncertainties also include the uncertainties discussed or identified in the public filings with the SEC and the AMF made by Sanofi, including those listed under "Risk Factors" and "Cautionary Statement Regarding Forward-Looking Statements" in Sanofi's annual report on Form 20-F for the year ended December 31, 2023. Other than as required by applicable law, Sanofi does not undertake any obligation to update or revise any forward-looking information or statements.