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Press Release

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New pivotal data at EHA 2021 reinforces sutimlimab as a first-in-class investigational C1s inhibitor with the potential to be the first approved treatment for hemolysis in people with cold agglutinin disease, a serious and chronic autoimmune hemolytic anemia

- Phase 3 data from the CADENZA study met the primary composite endpoint with statistical significance; secondary endpoint data were clinically meaningful
- Findings provide further evidence that sutimlimab results in rapid inhibition of C1-activated hemolysis within one week of treatment and had a sustained treatment effect throughout the study

PARIS – June 11, 2021 – Results from Part A of CADENZA, a pivotal Phase 3 double-blind, placebo-controlled study evaluating the safety and efficacy of sutimlimab in people with cold agglutinin disease (CAD) without a recent history of blood transfusion (within the prior six months), will be presented in an oral session at the European Hematology Association 2021 Congress. The data demonstrated treatment with sutimlimab resulted in rapid and sustained inhibition of C1-activated hemolysis in people with CAD, noted within one week of treatment, and clinically significant improvements in hemoglobin and fatigue when compared to placebo during the course of the study.

> *"Cold agglutinin disease causes the body's immune system to mistakenly destroy its healthy red blood cells. People living with cold agglutinin disease experience the crippling impact of chronic hemolysis that can cause severe anemia, profound fatigue and can have acute hemolytic crisis," said principal investigator and presenting author Professor Alexander Röth, M.D., Department of Hematology and Stem Cell Transplantation, University Hospital, University of Duisburg-Essen, Germany. "The positive evidence from the CADENZA trial demonstrate significant improvements in hemolysis and meaningful impact on key measures of anemia and fatigue."*

CADENZA is a second pivotal Phase 3 study investigating sutimlimab in the treatment of CAD. The primary efficacy outcome was the proportion of patients who met all three of the following components: improvement in hemoglobin ≥1.5 g/dL from baseline at treatment assessment timepoint, (average of Weeks 23, 25, and 26); avoidance of transfusions from Week 5 through Week 26; and avoidance of other CAD-related therapies beyond what was permitted from Week 5 through Week 26. The secondary efficacy measures assessed improvement from baseline in key indicators of the disease process including hemoglobin, bilirubin, lactate dehydrogenase (LDH) levels, and quality

of life as measured by Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Score.

> *"The results from CADENZA and data from the Phase 3 CARDINAL study, presented as a late-breaker at the American Society of Hematology congress in 2019, will be the basis of our filing with the European Medicines Agency. Together, the studies highlight the promising potential of sutimlimab to have a meaningful impact for people living with CAD," said Karin Knobe, M.D., Ph.D., Head of Development, Rare and Rare Blood Disorders, Sanofi. "Based on the robust clinical evidence we have to-date, sutimlimab significantly inhibits hemolysis and has the potential to be an important new treatment for CAD."*

CADENZA Phase 3 study data (final Part A) presented at EHA 2021

The CADENZA trial is a Phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of sutimlimab in patients with CAD without a recent history of blood transfusion (within the past 6 months). Eligible patients were randomized 1:1 to receive a fixed weight-based dose (6.5g or 7.5g) of sutimlimab or placebo via intravenous infusion on Day 0, Day 7 and then once every other week up to Week 26. The open-label Part B of the study is ongoing and will evaluate long-term safety as well as durability of response to sutimlimab in all participants with CAD.

Forty-two patients (mean age of 66.7 years) were enrolled and randomized to either sutimlimab (N=22) or placebo (N=20). Overall, 19 (86%) and 20 (100%) patients in the sutimlimab and placebo groups, respectively, completed Part A and continued into Part B. Three (14%) patients from the sutimlimab group discontinued Part A early due to adverse events.

Efficacy and safety data:

- Seventy-three percent (n=16) of patients treated with sutimlimab met the primary composite endpoint, demonstrating improvement in hemoglobin ≥1.5 g/dL from baseline at treatment assessment timepoint (Weeks 23, 25, and 26); avoidance of transfusions from Week 5 through Week 26; and avoidance of other CAD-related therapies beyond what was permitted from Week 5 through Week 26 compared to 15% (n=3) in the placebo group (Odds Ratio=15.9, 95% CI: 2.9 to 88.0, p<0.001).
- Data showed sutimlimab increased and sustained mean hemoglobin levels from baseline to treatment assessment timepoint (Week 26) representing a statistically significant least squares (LS) mean difference of 2.6 g/dL (p<0.001; 95% CI:1.8 to 3.4) when compared with placebo. Hemoglobin improved rapidly, with a LS mean increase from baseline of ≥1 g/dL by Week 1 and ≥2 g/dL by Week 3. Overall mean hemoglobin levels were maintained >11 g/dL from Week 3 through treatment assessment timepoint, demonstrating a sustained effect throughout the remainder of the treatment period.

- A statistically significant improvement in fatigue as measured by FACIT-Fatigue assessment was achieved in patients treated with sutimlimab when compared to the placebo group, 10.8 points versus 1.9, respectively, with a LS mean difference of 8.9 points ($p<0.001$; 95% CI:4.0 to 13.9). A 5 or greater point increase in FACIT-Fatigue score suggests a clinically important change. [1]
- Patients treated with sutimlimab had greater mean reductions in bilirubin, a key marker of hemolysis, from baseline to treatment assessment timepoint as compared with the placebo group (-22.1 µmol/L versus -1.8 µmol/L, respectively). Mean bilirubin levels were normalized below the upper limit of normal within 1 to 3 weeks in the sutimlimab group (upper limit of reference range 20.5 µmol/L) and maintained levels below the upper limit of normal to week 26.
- Treatment with sutimlimab led to meaningful improvements in LDH, an additional hemolysis marker, from baseline to treatment assessment timepoint compared to placebo (-150.8 U/L versus +7.6 U/L).
- Twenty-one patients (95.5%) in the sutimlimab group and 20 patients (100%) in the placebo group experienced at least one treatment emergent adverse event (TEAE).
- Three patients (13.6%) in the sutimlimab group experienced at least one treatment-emergent serious adverse event (TESAE) (n=4), including one TESAE assessed by the investigator as related to sutimlimab (cerebral venous thrombosis in a patient with a history of diabetes). One patient (5%) in the placebo group had three TESAEs.
- Treatment emergent adverse events reported more often in the sutimlimab group vs. placebo (difference of ≥ 3 patients between groups) were: headache (23% versus 10%), hypertension (23% versus 0%), rhinitis (18% versus 0%), Raynaud's phenomenon (18% versus 0%), and acrocyanosis (14% versus 0%). No deaths or meningococcal infections were reported.

Cold agglutinin disease, a rare and chronic condition

Cold agglutinin disease (CAD) is a rare, chronic autoimmune hemolytic anemia that causes the body's immune system to mistakenly attack healthy red blood cells and cause their destruction (hemolysis) via activation of the classical complement pathway. CAD patients may experience chronic anemia, profound fatigue, acute hemolytic crisis, and other potential complications, including an increased risk of thromboembolic events and early death.[2,3,4] CAD impacts the lives of an estimated 12,000 people in the U.S., Europe, and Japan.[5] Currently there are no approved therapies for CAD.

About CARDINAL Phase 3 Study

CARDINAL was the first of two pivotal Phase 3 studies investigating sutimlimab as a potential treatment for CAD. CARDINAL is an open-label, single-arm study to assess the efficacy and safety of sutimlimab in adult patients with CAD who received a recent blood transfusion. The CARDINAL data were presented in the Late-Breaking Abstracts Session at the *61st Annual Meeting of the American Society of Hematology* in December

2019 and are the basis of the Biologics License Application submission with the U.S Food and Drug Administration (FDA).

About Sutimlimab

Sutimlimab is an investigational, humanized monoclonal antibody that is designed to selectively target and inhibit C1s in the classical complement pathway, which is part of the innate immune system. By blocking C1s, sutimlimab inhibits the activation of the classical complement pathway with the goal of halting C1-activated hemolysis in CAD to prevent the abnormal destruction of healthy red blood cells. By selectively inhibiting the classical pathway upstream at C1s, sutimlimab does not inhibit the lectin and alternative complement pathways.

Sutimlimab has been granted Breakthrough Therapy by the U.S. Food and Drug Administration (FDA) and Orphan Drug status by the FDA, European Medicines Agency (EMA) and the Pharmaceuticals and Medical Devices Agency in Japan. Sutimlimab is currently under clinical investigation and has not been approved by any regulatory authority. Sanofi plans to resubmit its Biologics License Application with the U.S FDA in the second half of 2021.

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2. Broome C, et al. Increased risk of thrombotic events in cold agglutinin disease: A 10-year retrospective analysis. *Res Pract Thromb Haemost*. 2020;00:1–8.
3. Quentin A. Hill, Rajeshwari Punekar, Jaime Morales Arias, Catherine M Broome, Jun Su; Mortality Among Patients with Cold Agglutinin Disease in the United States: An Electronic Health Record (EHR)-Based Analysis. *Blood* 2019; 134 (Supplement_1): 4790.
4. Lauren C. Bylsma, Anne Gulbech Ording, Adam Rosenthal, Buket Öztürk, Jon P. Fryzek, Jaime Morales Arias, Alexander Röth, Sigbjørn Berentsen; Occurrence, thromboembolic risk, and mortality in Danish patients with cold agglutinin disease. *Blood Adv* 2019; 3 (20): 2980–2985.
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Sanofi Forward-Looking Statements

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