Long-term Inhibition of Complement C1s in Patients with Cold Agglutinin Disease: Lessons learned from a Named Patient Program

Supplemental data

- Sutimlimab (BIV009), developed by Bioverativ, a Sanofi Company.
- Sutimlimab is administered parenterally, no central venous access (port) is required unless peripheral venous access is compromised.
- The administered dose of sutimlimab was added to sodium chloride 0.9% and given as a 500 mL continuous infusion over the course of an hour.
- Sutimlimab was administered in a bi-weekly dose regimen.
- No premedication was used in the administration process of sutimlimab.
- After weekly administration of loading doses, patient visits were scheduled every two weeks for blood sampling and infusion therapy of sutimlimab. Blood draws were performed before sutimlimab infusions.

Figure S1. Laboratory course of patient 007.

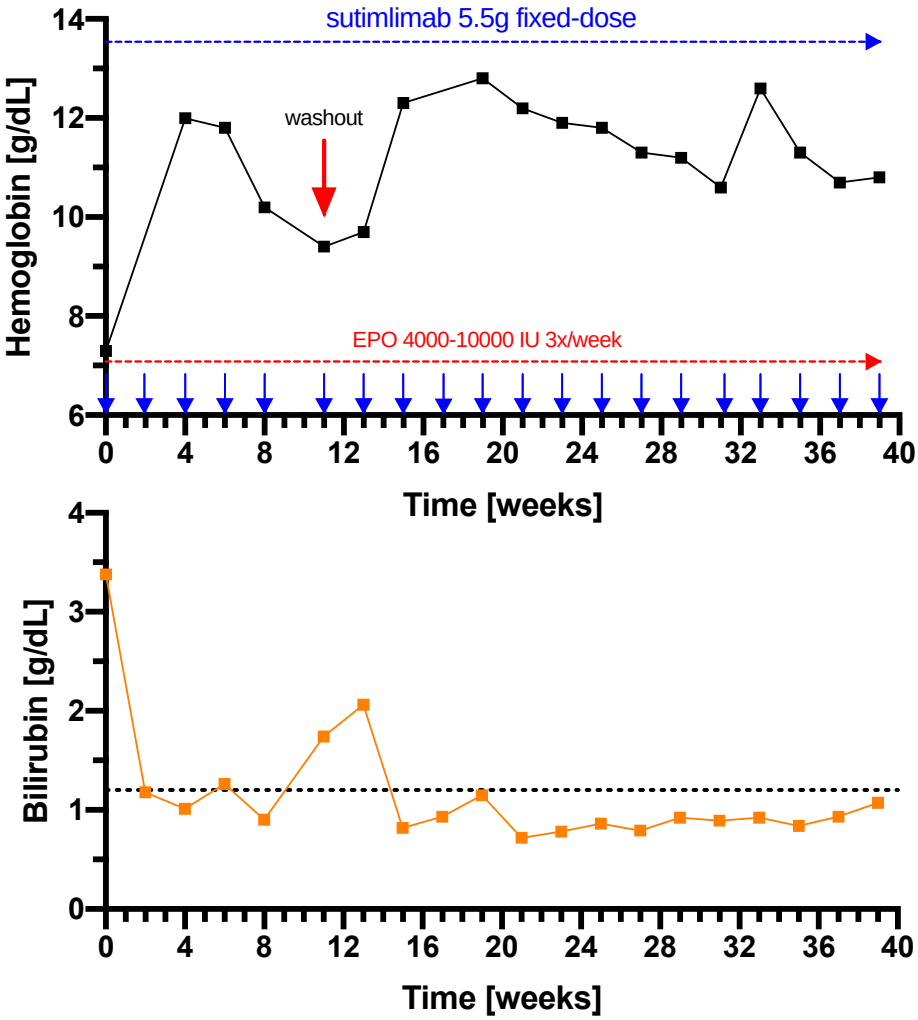

Figure S1. Patient 007 had an initial hemoglobin level of 7.3 g/dL, elevated levels of bilirubin and LDH and undetectable haptoglobin. The patient was re-started on sutimlimab following the phase 1b study using a 5.5 g fixed-dose bi-weekly regimen. Over the course of 4 weeks her hemoglobin level rose to 12 g/dL and hemolysis

parameters also normalized. Breakthrough hemolysis due to washout occurred after 4 doses of sutimlimab, her hemoglobin fell to a nadir of 9.4 g/dL and hemolysis parameters flared up (bilirubin > 2 mg/dL, haptoglobin below measurable limits). She then re-started the same sutimlimab regimen and her hemoglobin level again normalized over the course of 4 weeks, reaching a peak of 12.8 g/dL, and remained stable throughout the remainder of the NPP, however, haptoglobin levels were mostly below measurable limits, indicative of present - yet fully compensated - hemolysis.

Figure S2. Laboratory course of patient 005.

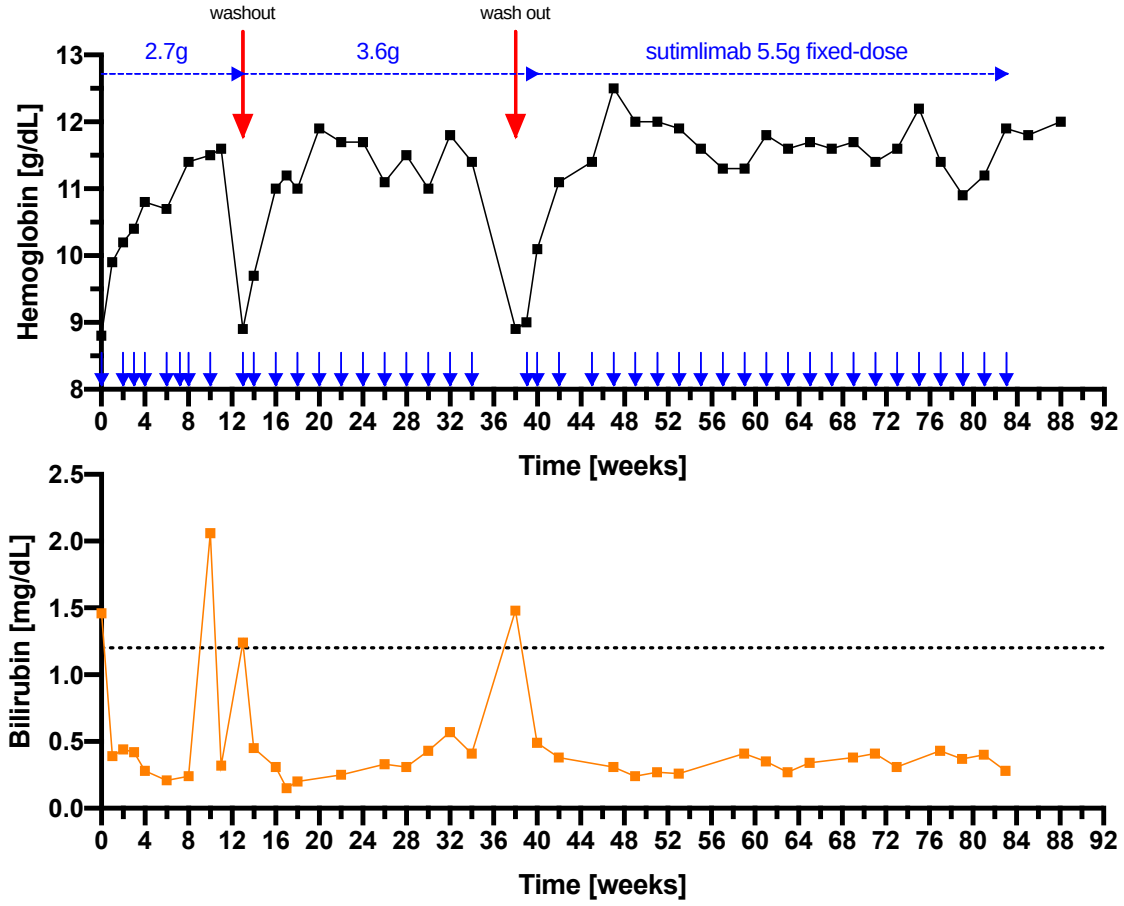

Figure S2. Patient 005 started with a hemoglobin level of 8.8 g/dL and active hemolysis (increased bilirubin and a haptoglobin level below measurable limits). She began re-treatment with sutimlimab 45 mg/kg (2.7 g) and after having received 3 weekly doses, her hemoglobin level increased by 2 g/dL to 10.8 g/dL and both bilirubin and haptoglobin levels normalized. After the 7th dose of sutimlimab, the patient experienced a drug washout associated biochemical breakthrough event (rise in CH50, bilirubin and LDH, decrease in C4, haptoglobin and hemoglobin) and the dose was subsequently increased to 60 mg/kg (3.6 g). As expected, hemolysis was rapidly abrogated and hemoglobin levels increased again. Five months later, after the withdrawal of sutimlimab for 4 weeks, she once again experienced breakthrough hemolysis due to washout of sutimlimab. After that, the dose was increased to a 5.5 g fixed-dose regimen resulting in suppressed hemolysis and stable hemoglobin levels throughout the remainder of the NPP.

Figure S3. Laboratory course of patient 003.

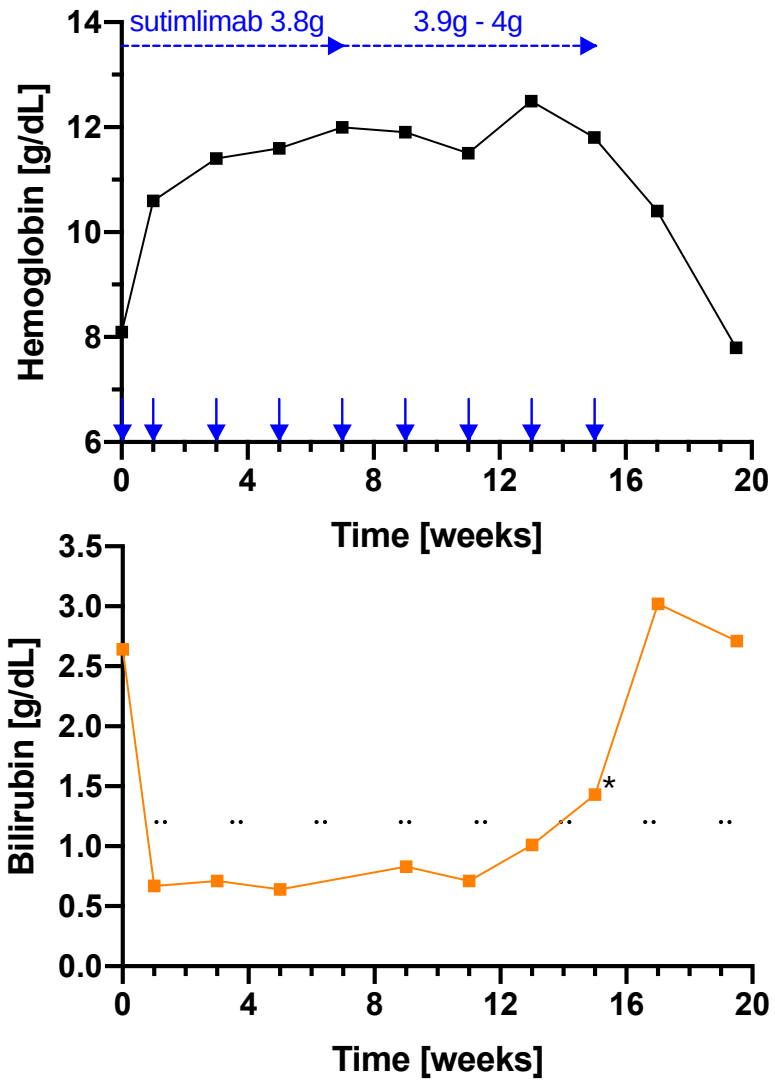

Figure S3. In patient 003, 60 mg/kg (3.8 g to 4 g) sutimlimab increased hemoglobin levels by 2.5 g/dL after 7 days (starting hemoglobin 8.1 g/dL), and normalized her hemoglobin, which reached a peak of 12.5 g/dL. The patient's haptoglobin levels remained below measurable limits, indicating fully-compensated hemolysis. *After the 9th dose of 60 mg/kg the patient experienced an increase in bilirubin to 1.43 mg/dL and LDH to 677 U/L indicating early biochemical evidence for breakthrough hemolysis due to underdosing in week 15 and sutimlimab treatment was subsequently withdrawn. Indeed, after two weeks, her levels of bilirubin and LDH increased further and her hemoglobin level dropped by 1.4 g/dL, confirming the breakthrough hemolysis event.
After the washout, the patient decided to stop sutimlimab and return to regular monthly transfusion therapy; she deemed this preferable to coming to the clinic twice a month for the sutimlimab infusion because she was a caretaker of her husband who was chronically ill with Alzheimer's disease. About 2.5 years later, the patient received 4 weekly doses of rituximab 1400 mg but did not respond to treatment.

Figure S4. D-dimer levels of patients included in the named patient program.

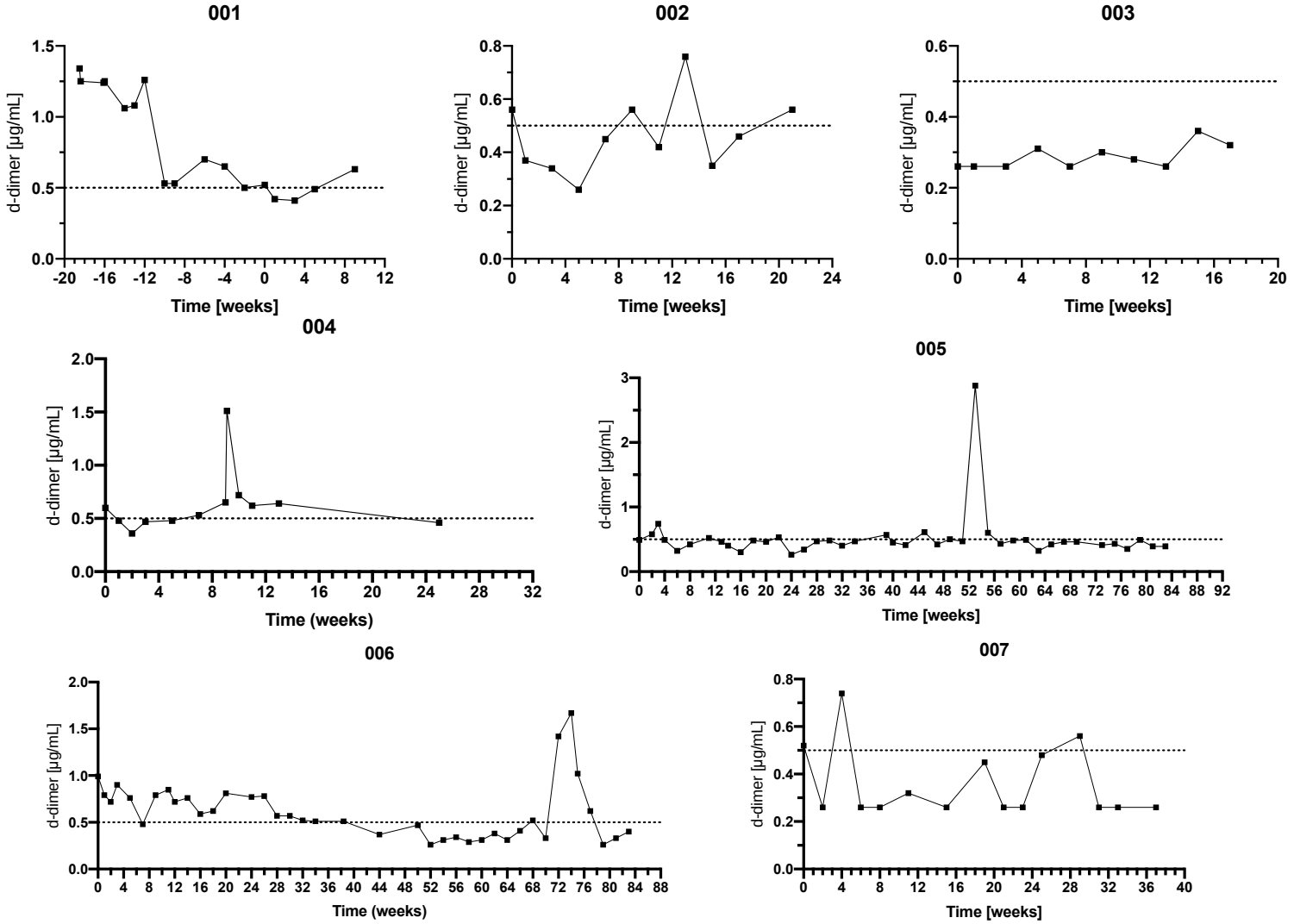

Table S1. Start and peak/nadir levels of hemoglobin (⊥ 12-16 g/dL), bilirubin (⊥ 0.0-1.2 mg/dL), LDH (⊥ < 250 U/L) and haptoglobin (⊥ 30-200 mg/dL).

patient	**hemoglobin start** [g/dL]	**hemoglobin peak** [g/dL]	**bilirubin start** [mg/dL]	**bilirubin nadir** [mg/dL]	**LDH start** [U/L]	**LDH nadir** [U/L]	**haptoglobin start** [mg/dL]	**haptoglobin peak** [mg/dL]
001	7,7	12,2	1,59	0,77	336	334	<12	<12
002	7,9	13,4	1,40	0,25	322	130	<12	152
003	8,1	12,5	2,64	0,64	335	238	<12	<12
004	7,4	13,2	5,19	0,44	532	148	<12	146
005	8,8	12,5	1,46	0,15	232	154	<12	227
006	7,1	12,0	1,75	0,22	406	216	<12	80
007	7,3	12,8	3,38	0,72	825	177	<12	62,8
median	**7,7**	**12,5**	**1,75**	**0,40**	**336**	**177**	**<12**	**80**

Table S2. Adverse events, according to the system organ class categorization.

SYSTEM ORGAN CLASS	001	002	003	004	005	006	007	
Blood and lymphatic system disorders								
Cardiac disorders					4	1		
Congenital, familial and genetic disorders								
Ear and labyrinth disorders					2		1	
Endocrine disorders								
Eye disorders		1						
Gastrointestinal disorders			1			6		**7**
General disorders and administration site conditions			1		3	3	3	**10**
Hepatobiliary disorders								
Immune system disorders								
Infections and infestations					3	1		
Injury, poisoning and procedural complications								
Investigations								
Metabolism and nutrition disorders			2					
Musculoskeletal and connective tissue disorders		1			1	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					2			
Nervous system disorders				1	2	1	1	
Pregnancy, puerperium and perinatal conditions								
Psychiatric disorders								
Renal and urinary disorders	1			1		1		
Reproductive system and breast disorders								
Respiratory, thoracic and mediastinal disorders					1	1	1	
Skin and subcutaneous tissue disorders		2	1	1	3	2	1	**10**

Social circumstances							
Surgical and medical procedures						1	
Vascular disorders					1		
Product issues							
total	**1**	**4**	**5**	**3**	**22**	**18**	**8**