Supplemental Table 1: Full list of in- and exclusion criteria

Inclusion criteria - Positive (≥1+) monospecific antiglobulin test for C3b and/or C3d *with/without* positivity for IgM OR strongly positive (≥3+) monospecific antiglobulin test for C3b and/or C3d *with* positivity for IgG - Indication for a transfusion with at least 2 red packed cell concentrates based on the clinical assessment by the hematologist in charge - Hemoglobin value at least < 5 mmol/L (8 g/dL) with/without clinical symptoms - Clinical signs of hemolysis: not-detectable haptoglobin (mandatory) and increased lactate dehydrogenase (LDH) eventually combined with hyperbilirubinemia (increased direct and/or indirect bilirubin), lactate. - Age ≥ 18 years - Written informed consent - Women of child bearing potential must have had a negative serum pregnancy test 7 days prior to the start of study drug

Exclusion criteria
- History of arterial and/or venous thromboembolic events in the absence of an actual treatment with Vitamin K-antagonists
- Concomitant use of therapeutic doses of heparin
- Female patients who are pregnant or breast feeding or adults of reproductive potential who are not using effective birth control methods. If barrier contraceptives are being used, these must be continued throughout the trial by both sexes. Oral contraceptives only are not acceptable.
- Patients with known HIV seropositivity or chronic active hepatitis
- Patients who have any severe and/or uncontrolled medical condition or other conditions that could affect their participation in the study such as:
  o cerebrovascular accidents ≤ 6 months before study drug start
  o uncontrolled hypertension

Supplemental Table 2

Case	Recent AIHA treatments
1	Prednisone, rituximab
2	Cyclosporine, mycophenolate, prednisone, rituximab
3	Prednisone, IVIG, rituximab, vincristine
4	Rituximab, bendamustine, prednisone, IVIG
5	Prednisone, darbepoetin, IVIG, rituximab
6	Darbepoetin
7	Prednisone, methylprednisone, rituximab, IVIG, darbepoetin, ibrutinib
8	Prednisone, rituximab, darbepoetin
9	Rituximab, bortezomib, dexamethasone, epoetin bèta
10	Dexamethasone, prednisone, darbepoetin

Supplemental Table 2: AIHA treatments for each patient in in the 2 months before inclusion in the current trial.

Supplemental Table 3

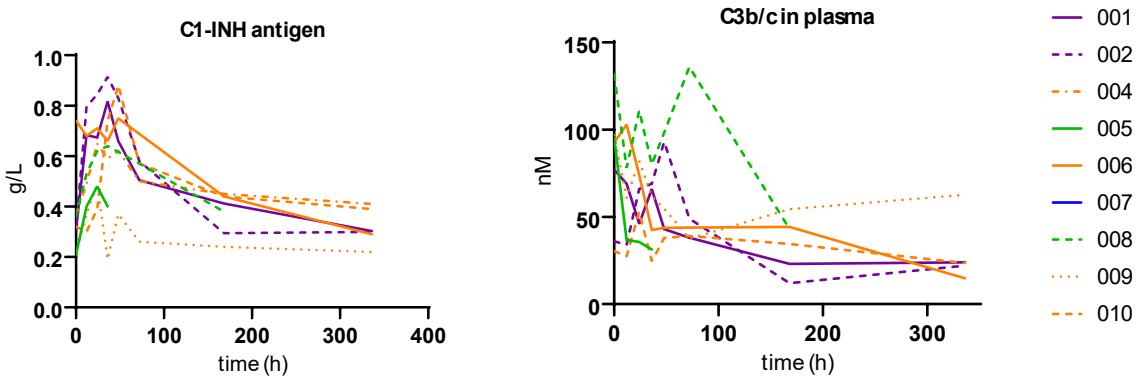
Adverse events	**Amount of patients**	**Investigator causality assessment to study medication**
<u>Grade 1-2</u>		
Headache	2	probable
Fever	2	probable
Back pain	2	possible
Non-cardiac chest pain	3	possible (2x), not related (1x)
Dry cough	2	possible
Flushing	1	possible
Dizziness	1	possible
Diarrhea	1	possible
Abdominal pain	2	possible (1x), not related (1x)
Flu-like symptoms	1	possible
Palpitations	1	not related
Fatigue	1	not related
Esophagitis	2	not related
Conjunctivitis	1	not related
Edema limbs	1	not related
Hematuria	1	not related
Epistaxis	1	not related
Oral candidiasis	1	not related
Dysarthria	1	not related
Anxiety, depression	1	not related
Sore throat	1	not related
Muscle atrophy	1	not related
Somnolence	1	not related
Tingling sensation in fingers	1	not related
Worsening hemolytic anemia	1	not related
White papillae tongue	1	not related
Total	**34 events in 7 patients**	
<u>Grade 3- 4</u>		
Constipation	2	not related
Hypertension*	1	not related
Hyponatremia*	1	not related
Dyspnea†	1	not related
Worsening hemolytic anemia	1	not related
Total	**6 events in 2 patients**	

Supplemental table 3: Overview of all adverse events (AE)

* Related to renal faillure

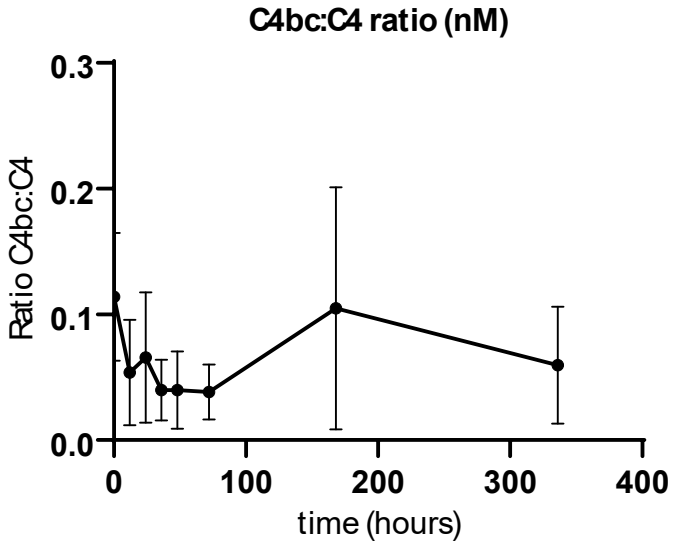
† Hypersensitifity reaction to pentamidine inhalation

Supplemental Figure 1



Supplemental Figure 1: C1-INH response does not depend on bodyweight. Exploratory analysis of C1-INH antigen (a) and C3b/c (b) levels for different U/kg bodyweight in the first dose. Green: 60-79 U/kg; orange: 80-99 U/kg; blue: 100-199 U/kg; purple: >120 U/kg.

Supplemental Figure 2



Supplemental Figure 2: Ratio between C4b/c and C4. The ratio between C4b/c and C4 does not change throughout the trial. Significance test there is only a low amount of C4b/c present compared to C4. Data expressed as median + IQR, significance tested using mixed effect analysis with Geisser-Greenhouse correction and Holm-Šídák's multiple comparisons test.