

Results of COBALT, a Phase II clinical trial of Coversin in PNH

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Background

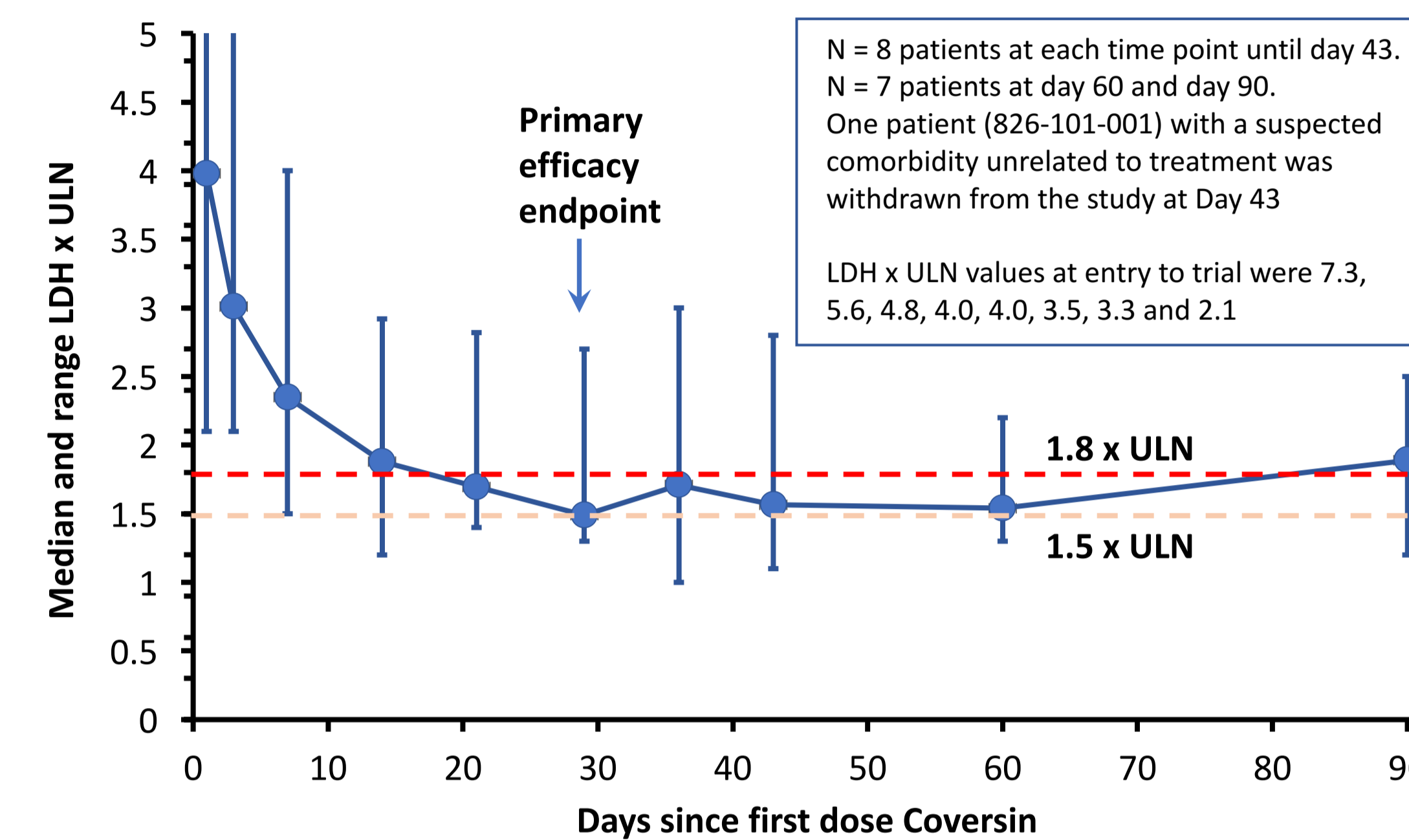
- Coversin, a 17kDa protein, binds complement C5 with high affinity (Kd 1nM) preventing cleavage to C5a and C5b and formation of the membrane attack complex
- This mode of action is similar to eculizumab, a monoclonal antibody which has been approved for treatment of paroxysmal nocturnal haemoglobinuria (PNH) since 2007
- Coversin's inhibitory activity has been shown to be unaffected by the single amino acid C5 polymorphism which makes some patients resistant to eculizumab
- Eculizumab is administered by i.v. infusion every two weeks which may interfere with the life-style, work and personal privacy of patients
- Coversin is suitable for subcutaneous injection and patients can self-administer

Aims

- The aims of COBALT was to assess the safety and tolerability of Coversin, the efficacy* of the dosing regime and whether self-injection is well accepted

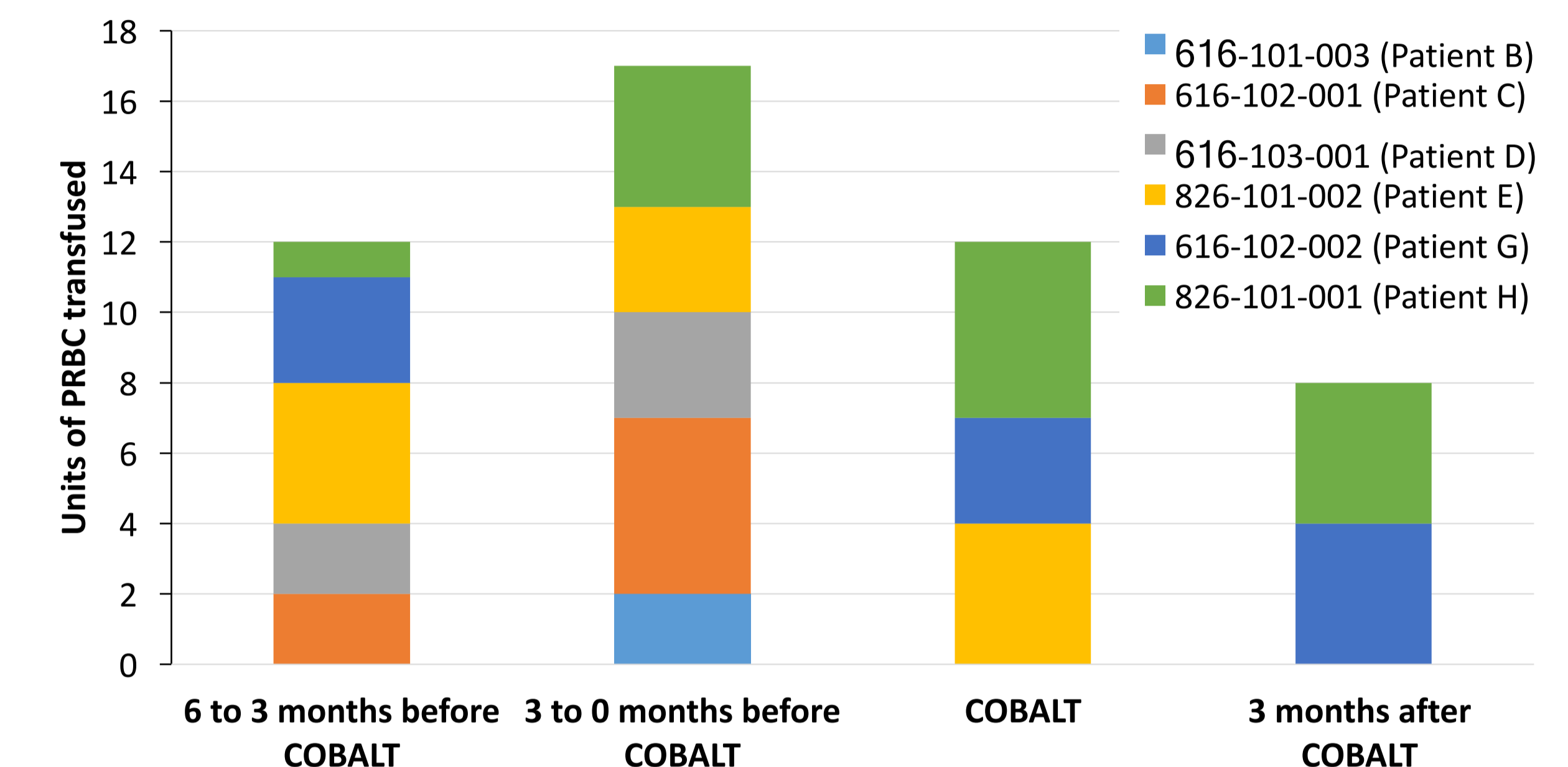
*The primary efficacy endpoint was defined as reduction in lactate dehydrogenase (LDH) to ≤ 1.8 times ULN for the investigators reference laboratory at day 28.

COBALT Intention to Treat (ITT): LDH



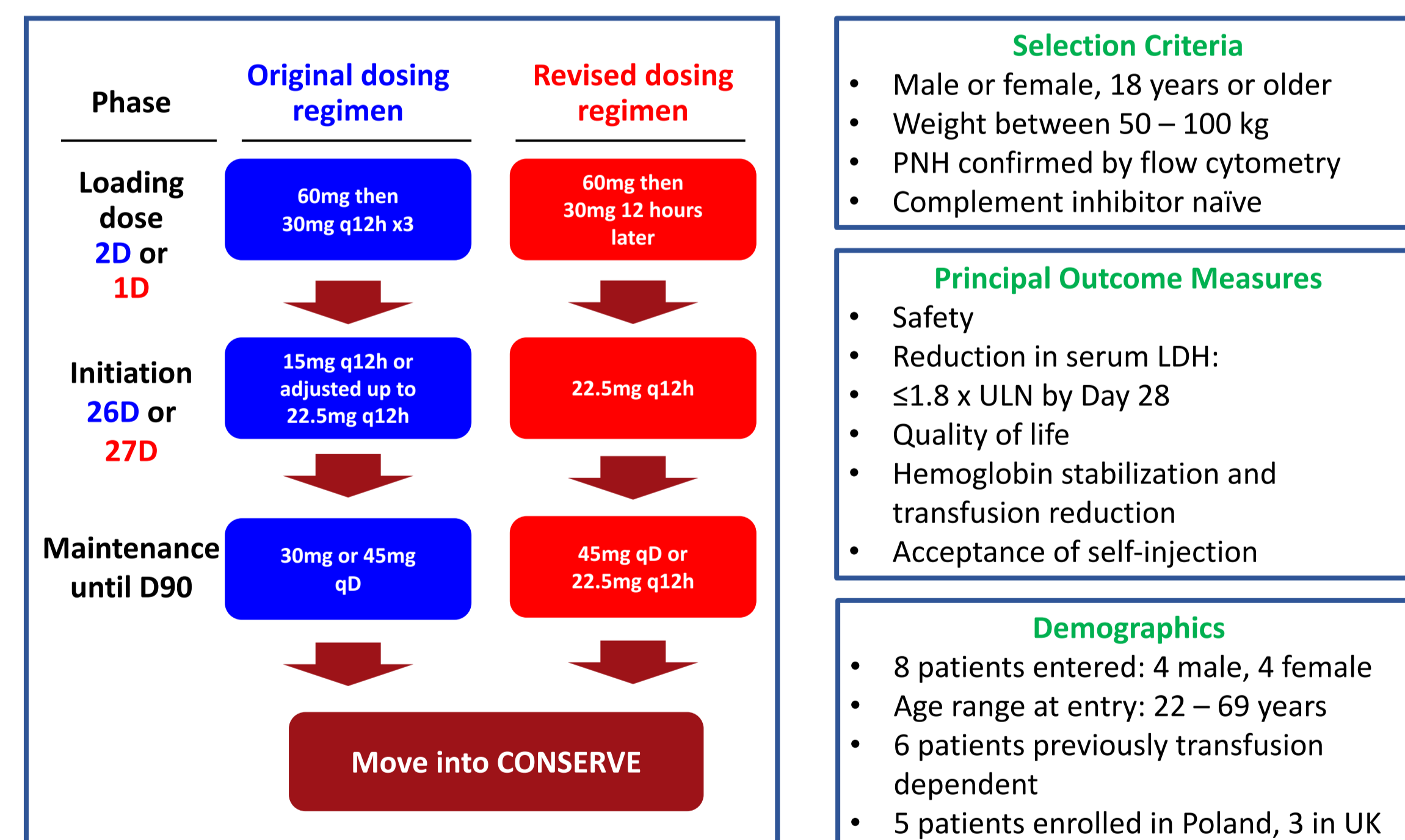
LDH x ULN values at Day 28 were: 1.4, 2.2, 2.3, 1.3, 1.4, 2.7, 1.6, 1.3; LDH x ULN values at Day 60 were: 1.5, 2.1, 1.8, 2.2, 1.5, 1.4, 1.3; LDH x ULN values at Day 90 were: 1.6, 2.4, 2.0, 2.5, 1.9, 1.5, 1.2

COBALT ITT Result: Transfusion



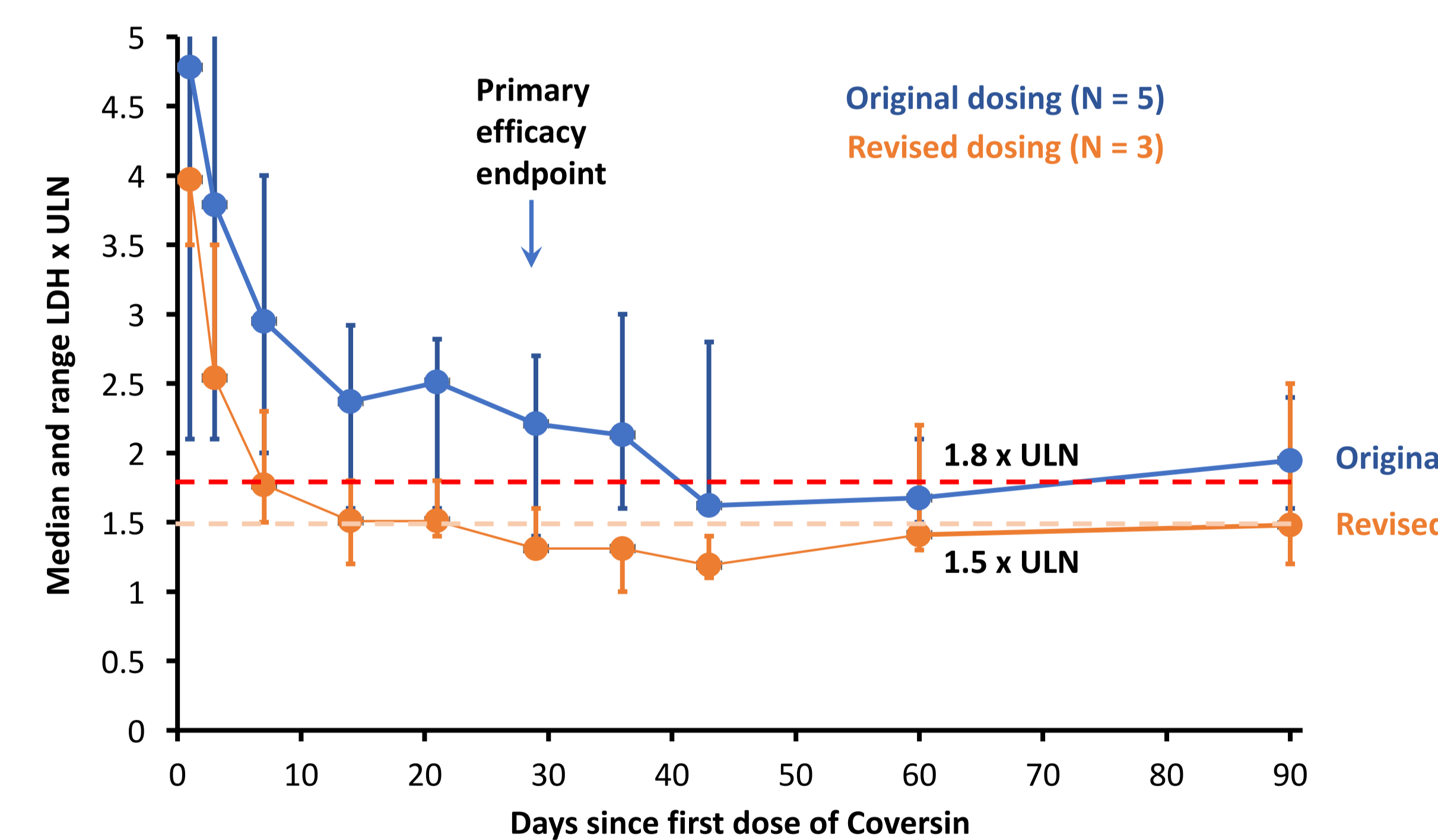
Six patients transfused prior to entering COBALT; 3 became transfusion independent in COBALT

COBALT Trial Design



5 patients received original dosing regimen and 3 patients received the revised dosing regimen

COBALT Original & Revised dosing: LDH



COBALT Safety

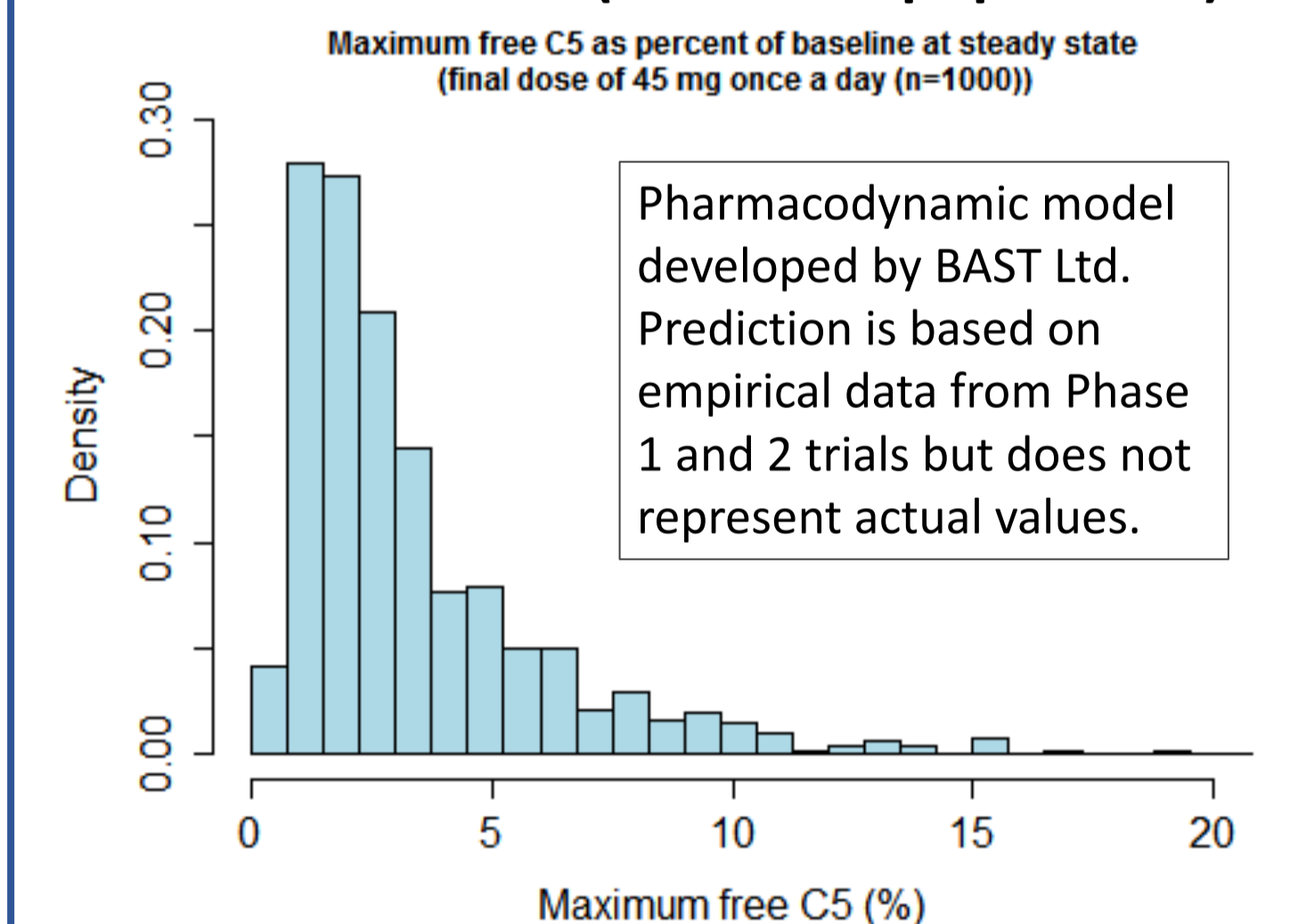
Summary of Treatment emergent AEs

Event	Related	Possibly Related
Injection site haematoma (moderate)	1	
Injection site reaction (Grade 2)		8
Abdominal discomfort (mild)	1	
Oral paraesthesia (mild)		1
Rash (moderate)		2
Pruritis (moderate)		1
Headache (mild)		1
Osteoarthritis (moderate)		1
Hypophosphataemia (mild)		2
Hypoproteinaemia (mild)		2
TOTAL	2	18

- 4 SAEs but no treatment related SAEs
- The most frequent AEs were mild self limiting injection site reactions (not shown in Table)

Model of C5 inhibition

Maximum free C5 (simulated population)

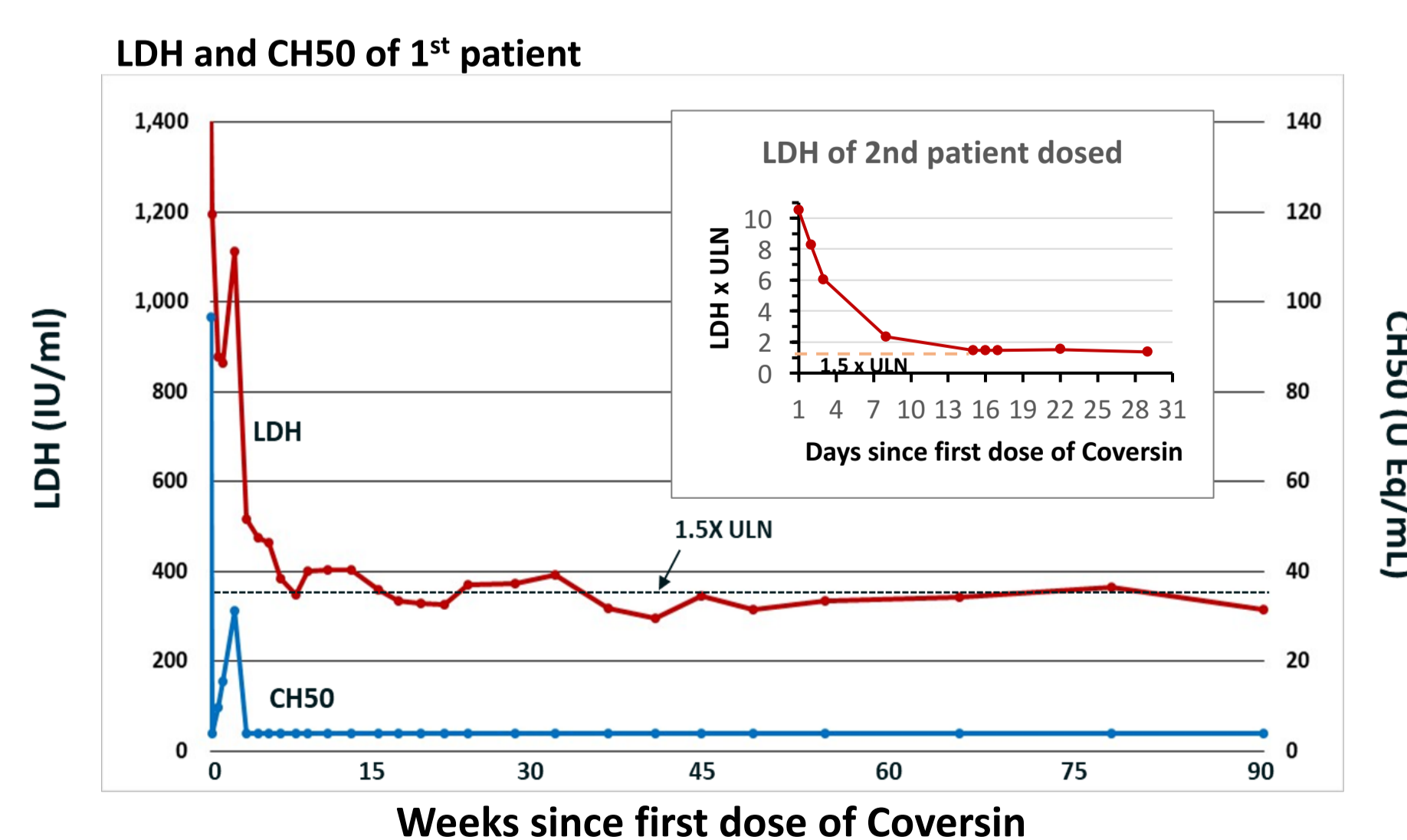


Threshold	45mg QD
Proportion of patients <5 % free C5	80.7
Proportion of patients <10 % free C5	96.9

Eculizumab Resistance: CONSENT-1 and CONSENT-2*

- Two patients with C5 polymorphisms conferring resistance to eculizumab have now been treated with Coversin (Patient 1: >2 years; Patient 2: approx. 4 weeks)
- Both patients responded to Coversin treatment
- Latest LDH from 1st patient is 1.5 x ULN (at 28 months)
- Initial data from a 1st patient, treated in USA, under the revised dosing regimen with LDH 10.5 x ULN at baseline has shown a rapid reduction in LDH to 1.4 x ULN at Day 29 [see Figure on right]
- Ongoing resistance study (CONSENT) open in Holland and the USA and recruiting

*Patients enrolled in CONSENT were not part of the Phase II COBALT trial



LDH x ULN for the two eculizumab resistant patients treated with Coversin in CONSENT trials

Conclusions

- Coversin daily subcutaneous injection showed positive safety profile and clinical response in PNH patients with or without C5 eculizumab resistant polymorphism
- Revised, simplified dosing regimen, applied to last 3 patients in COBALT and 2nd eculizumab resistant patient, showed rapid initial reduction in LDH and clinical response
- All patients self-injected and all patients who completed COBALT (N = 7) opted to stay on Coversin at the end of the trial
- More than 120 months of safety data from patients on Coversin now available
- New dosing regimen being used in newly open Phase III CAPSTONE PNH trial