Natural history of AAV5 neutralising antibodies in adults with haemophilia B during ≥6-month screening and lead-in to the HOPE-B trial with etranacogene dezaparvovec gene therapy

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Introduction

- Testing for binding or neutralising antibodies (NAbs) to adeno-associated virus (AAV) is part of the laboratory assessment of people with haemophilia considering AAV-based gene therapy
- We evaluated the natural history of NAb titres to AAV serotype 5 (AAV5) in adult males ≥18 years old with haemophilia B (factor IX [FIX] ≤2%) during the lead-in period of the pivotal HOPE-B trial (NCT03569891) prior to infusion of etranacogene dezaparvovec (CSL222, HEMGENIX®)[1–3]

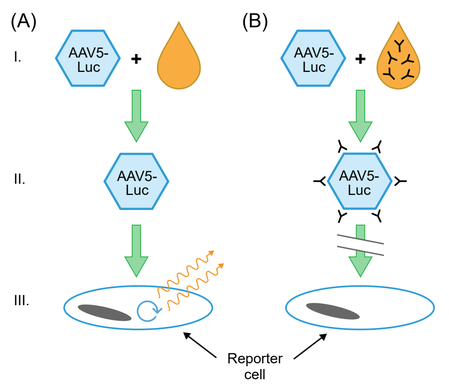
Objective

- **To characterise NAbs, immunoglobulin (Ig) G and IgM anti-AAV5 binding antibody changes over ≥6 months (lead-in period of HOPE-B)**

Methods

- A total of 67 adult male participants with severe or moderately severe haemophilia B (FIX ≤2%) were enrolled into the lead-in period of HOPE-B
- During the lead-in period, visits for AAV5 antibody testing were as follows: screening and then approximately every 1–2 months over a period of ≥6 months and including a final baseline visit prior to gene therapy infusion[1,4]
- AAV5 NAbs were measured using a cell-based luminescence reporter AAV5 NAb assay with 7 serum dilutions and a limit of detection of 7 (Figure 1AB)
- IgG or IgM anti-AAV subclasses were measured using a separate ELISA with a limit of detection of 50 (Figure 1C)

Figure 1. AAV5 TI/NAb assay (A, B)[a] and the anti-AAV5 IgG and IgM ELISA (C)[b]



(**A**) In the absence of AAV5 NAbs, the unaffected reporter vector (I) can transduce the reporter cells (II), thereby establishing luciferase expression, which can be measured by bioluminescence (III). (**B**) AAV5 NAbs present in the participant's serum bind to reporter vector particles, impairing their ability to transduce the reporter cells and resulting in lack of luciferase expression. (**C**) I) HRP-labelled, isotype-specific detection antibody in the respective antigen capture ELISA. II) IgG or IgM anti-AAV5 in the participant's serum binds to III) AAV5 bound to the microtitre plate.

[a]NAb titre was calculated as the midpoint of the serum neutralising activity titration response curve (IC_{50}); [b]IgG or IgM titre was defined as the reciprocal serum dilution at the technical cutpoint of the assay.
AAV5, adeno-associated virus serotype 5; ELISA, enzyme-linked immunosorbent assay; HRP, horseradish peroxidase; IgG, immunoglobulin G; IgM, immunoglobulin M; Luc, luciferase; NAb, neutralising antibody; TI, transduction inhibition.

Table 1. Demographic characteristics in the lead-in safety population

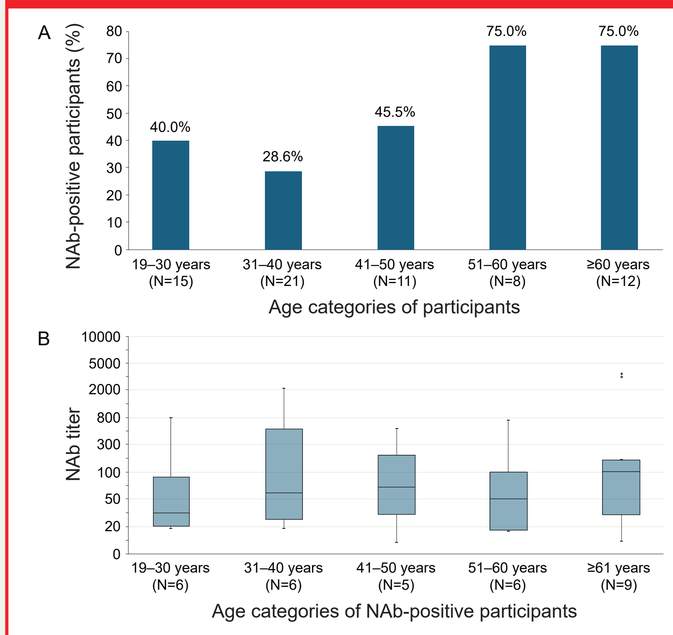
Characteristic	NAb+	NAb−	All pts (N=67)
NAb status, n (%)	32 (47.8)	35 (52.2)	
Age, mean (SD) years	48 (17.5)	38 (13.2)	43 (16.2)
Range	19–78	21–73	19–78
Severe HB (FIX <1%)[a]	26 (81.3)	30 (85.7)	56 (83.6)
Moderately severe HB (FIX 1–2%)[a]	6 (18.8)	5 (14.3)	11 (16.4)
Prior hepatitis B, n (%)	10 (31.3)	3 (8.6)	13 (19.4)
Prior/resolved HCV (HCV RNA−)[b], n (%)	23 (71.9)	14 (40.0)	37 (55.2)
Ongoing HCV (HCV RNA+)[b], n (%)	1 (3.1)[c]	0	1 (1.5)
HIV+, n (%)	3 (9.4)	1 (2.9)	4 (6.0)

[a]At diagnosis; [b]At screening; [c]Participants positive at screening had detectable hepatitis C virus RNA. This participant was positive at screening while undergoing HCV anti-viral therapy with glecaprevir/pibrentasvir and was negative at the L-Final visit (21 days before etranacogene dezaparvovec administration).
FIX, factor IX; HB, haemophilia B; HIV+, human immunodeficiency virus-positive; pts, participants; SD, standard deviation

Results

- At screening, 48% (32/67) of enrolled patients had detectable NAbs (NAb+; Table 1), with a median titre of 58 (range: 9–3440)
- The median duration of the patient NAb data collection period was 240 days (range: 1–360)
- Nab+ patients were older than NAb-negative patients at baseline (p=0.0065); however, no association between titre and age was observed (Figure 2AB)
- The median intra-patient coefficient of variation of NAb titres over time was 25% (range: 2–154%) and patient NAb titres remained stable during the lead-in relative to screening (Table 2 and Figure 3)
- For patients with detectable anti-AAV5 NAbs and IgG at screening (N=22), there was a high correlation of titres (median r=0.96; range: 0.92–0.99) (Figure 4)
- One patient clearly seroconverted to NAb positivity, with NAb and IgM undetectable at screening and titres of 82 and 139, respectively, 4 months later (Figure 5); another converted to NAb positivity (NAb titre: 13.7) after 8 months without IgM Abs being detected

Figure 2. NAb+ status by age category (A) and NAb titre by age category (B)



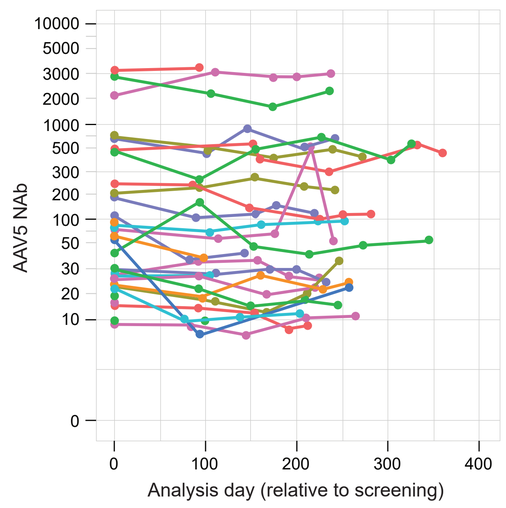
*NAb titre measure considered to be an outlier.
NAb, neutralising antibody

Table 2. AAV5 NAb titre agreement between screening and pre-dose baseline visit in patients with paired data (N=19)[a,b]

	Screening	Pre-dose baseline visit
N	19	19
Mean (SD)	292.0 (482.25)	325.5 (730.21)
Median	88.2	57.8
(range)	(8.8–2020.4)	(8.5–3212.3)
ICC (95% CI)[c]	0.89 (0.741, 0.957)	

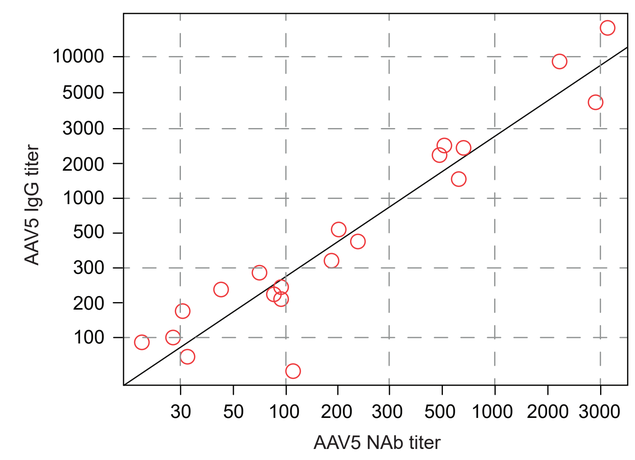
[a]Only patients with paired data included; [b]The time period between the screening visit and the median pre-dose baseline visit duration was 246 days (range: 216–360); [c]The ICC was calculated using a type 3 sums of squares from an analysis of variance model.
AAV5, adeno-associated virus serotype 5; CI, confidence interval; ICC, intraclass correlation coefficient; NAb, neutralising antibody; SD, standard deviation

Figure 3. Individual NAb values over the lead-in period in participants who were NAb+ at screening (N=26)[a]



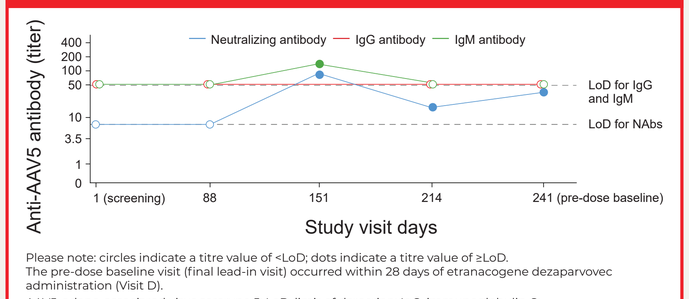
[a]Values are given for each participant who was NAb+ at screening and during the lead-in period of ≥6 months. AAV5, adeno-associated virus serotype 5; NAb, neutralising antibody; NAb+, neutralising antibody-positive

Figure 4. Correlation of NAb and IgG titres at screening in participants with values >LoD (N=20)



Please note: this figure does not include 2 participants who had detectable AAV5 IgG by confirmatory assay but whose titre assay result was <LoD.
AAV5, adeno-associated virus serotype 5; IgG, immunoglobulin G; LoD, limit of detection; NAb, neutralising antibody.

Figure 5. Longitudinal NAb, IgM, and IgG levels in participant who seroconverted



Please note: circles indicate a titre value of <LoD; dots indicate a titre value of ≥LoD.
The pre-dose baseline visit (final lead-in visit) occurred within 28 days of etranacogene dezaparvovec administration (Visit D).
AAV5, adeno-associated virus serotype 5; LoD, limit of detection; IgG, immunoglobulin G; IgM, immunoglobulin M; NAb, neutralising antibody

Conclusions

- **AAV5 NAbs were stable over ≥6 months. NAbs were highly correlated with IgG anti-AAV5 Abs, although titre values differed**
- **These data can help inform patient-management decisions for etranacogene dezaparvovec**

During ≥6 months:

- NAb levels were stable over a median lead-in period of 240 days
- Anti-AAV5 NAbs and total IgG Abs were highly correlated
- Seroconversions were infrequent

Disclosures

RK has received consultancy fees from Sobi, Sanofi, Roche/Chugai, Pfizer, Octapharma, Bayer, BioMarin, Takeda, Novo Nordisk, Grifols, Biotest and CSL Behring; and has received research funding from Bayer and consulting/lecture fees from Bayer, BioMarin, Spark, Novo Noridsk and Pfizer; **MR** has received research support from Bayer, BioMarin, CSL Behring, Genentech, Grifols, Hema Biologics, LFB, Novo Nordisk, Octapharma, Sanofi, Spark, Takeda and uniQure; consultancy fees from Catalyst Biosciences, CSL Behring, Genentech, Hema Biologics, Kedrion, Novo Nordisk, Pfizer, Sanofi, Takeda and uniQure; and sits on the Board of Directors for Foundation for Women and Girls with Blood Disorders and Partners in Bleeding Disorders; **NK** has received grant/research support from and consultancy fees from uniQure, Biomarin and Novo Nordisk; **WM** has received grant/research support from Bayer, Biotest, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer and Takeda/Shire; consultation/speaker fees from Bayer, Biomarin, Biotest, CSL Behring, Chugai, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi and Takeda/Shire; and consultation fees from Bayer, Biomarin, Biotest, CSL Behring, Chugai, Freeline, LFB, Novo Nordisk, Octapharma, Pfizer, Regeneron, Roche, Sanofi, Sobi, Takeda/Shire and uniQure; **SWP** has received consultancy fees from Apcintex, ASC Therapeutics, Bayer, BioMarin, CSL Behring, GeneVentiv, HEMA Biologics, Freeline, LFB, Metagenomi, Novo Nordisk, Pfizer, Poseida Therapeutics, Roche/Genentech, Sanofi, Takeda and Spark Therapeutics; research funding from Siemens and YewSavin; and is a member of scientific advisory committees for GeneVentiv and Equilibra Bioscience; **PvdV** has received consultation fees from Bayer; **RK** has received research funding from Bayer; and consulting or lecture fees from Bayer, BioMarin, Spark, Novo Noridsk and Pfizer; **DD**, **NG**, **PEM**, **BS** and **JT** are employees of CSL Behring, King of Prussia, PA, USA; **SLQ** is an employee of CSL Behring Europe, Hattersheim am Main, Germany.

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