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Effect of Combined Administration of IVIg and the Classical Complement Inhibitor ANX005, a Human Anti-C1q Monoclonal Antibody, in Guillain-Barré Syndrome (GBS)

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Preliminary Results from the Drug Drug Interaction (DDI) Clinical Study Conducted in GBS subjects in Bangladesh and Denmark

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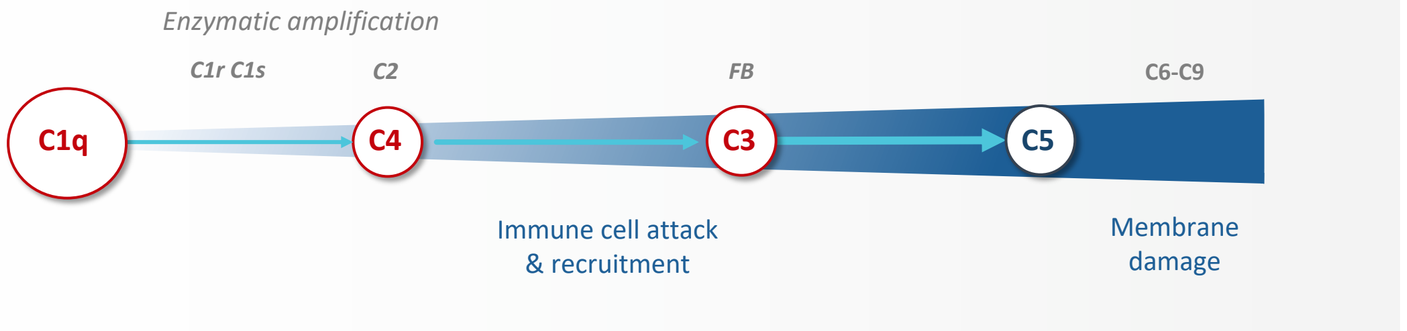
Disclosures

- T Harbo: received honorarium or fees for consulting from Annexon Biosciences, USA
- Z Islam: received funding/grant support from Fogarty International Center, Department of Health and Human Services, National Institutes of Health, USA and Annexon Biosciences, USA
- QD Mohammad: received honorarium or fees for consulting from Annexon Biosciences, USA
- N Papri, I Jahan, S Hayat, A Rahman, Gurudas Mondal and Sadekur Rahman Sarkar have no potential conflicts of interest to disclose
- H-A Kroon, P Lin, A Grover, E Humphriss, and S Keswani are employees of Annexon Biosciences and may hold Annexon Biosciences stock and/or stock options

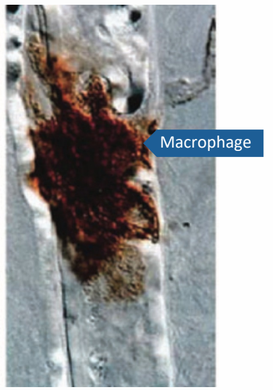
Inhibiting C1q Upstream with ANX005 Prevents Downstream Activation of all Tissue Damaging Components in GBS



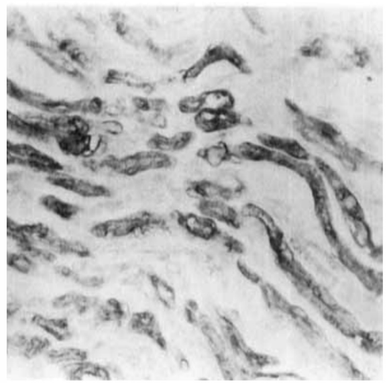
POTENTIAL EFFICACY ADVANTAGE: Shuts down all tissue-damaging components of classical pathway (C1q, C4, C3, C5, C9)[1]

POTENTIAL SAFETY ADVANTAGE: Allows normal immune functions of lectin and alternative complement pathways[1]

C3d deposition on Node of Ranvier[2]



Macrophage infiltration[2]



C5b-9 deposition on individual nerve fibers[2]

[1] *Annexon Data on File*
[2] *Willison. Journal of the Peripheral Nervous System 17(S):3–8 (2012)*

Open Label Drug-Drug Interaction (DDI) Study in GBS Subjects from Bangladesh and Denmark

First trial in GBS evaluating subjects from Bangladesh and Denmark with single treatment regimen

TRIAL OBJECTIVES:

- **Safety / Tolerability / PK**
- **C1q Target Engagement / PD**
  N = 14

METHOD:

- Open Label DDI study of a single dose of ANX005 75 mg/kg given during first 3 days of standard IVIg treatment with 26 weeks follow-up
- Adults with GBS Disability Score (GBS-DS) ≥3 with onset of symptoms ≤14 days

PRELIMINARY ANALYSIS:

- Safety and Tolerability assessed against IVIg label and safety profile ANX005 established in previously conducted GBS Phase 1b, Normal Healthy Volunteers and ongoing Phase 2 Huntington's Disease study
- PK and PD compared against subjects receiving single dose ANX005 75 mg/kg in earlier phase 1b study in Bangladesh (N=10)
- Patient clinical outcomes assessed by GBS-DS, MRC-sum score, RODS, Neurofilament Light (NfL) at each visit
- Open label design and not powered for formal outcome analysis or comparison to treatment with IVIg or ANX005 alone

Preliminary Results: Safety / Tolerability Data

Combined use of ANX005 and IVIg well-tolerated

- All 14 GBS subjects experienced ≥ 1 treatment emergent adverse events (TEAE), mainly grade 1 and 2
- One subject reported one serious adverse event (SAE) related to a second dose of IVIG following a treatment related fluctuation
- Two subjects reported two grade 3 TEAE (elevated CPK and LFT) related to the natural history of GBS

EVENTS OF INTEREST:

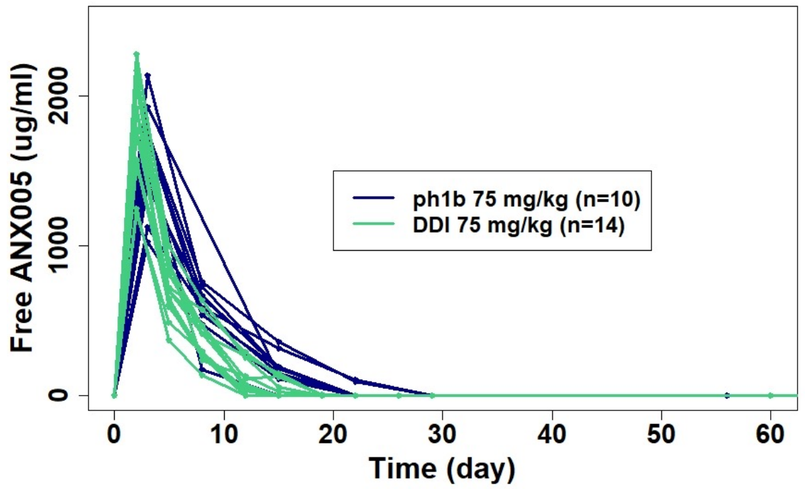
- Infusion related reactions: transient skin rash; well managed
- Infections with encapsulated bacteria: none

CATEGORY	ANX005 + IVIG (N=14) N (%)
Any TEAE	14 (100%)
Related to ANX005	
Serious Adverse Events	0
Infusion Related TEAE	8 (57%)
Pain – injection site	0
Pain – musculoskeletal	0
Unrelated to ANX005	
Serious Adverse Events	1 (7%)
	Fever Unknown Focus Pulmonary Embolus
Grade 3 CTCAE	CPK and LFT

Preliminary Results: PK and PD

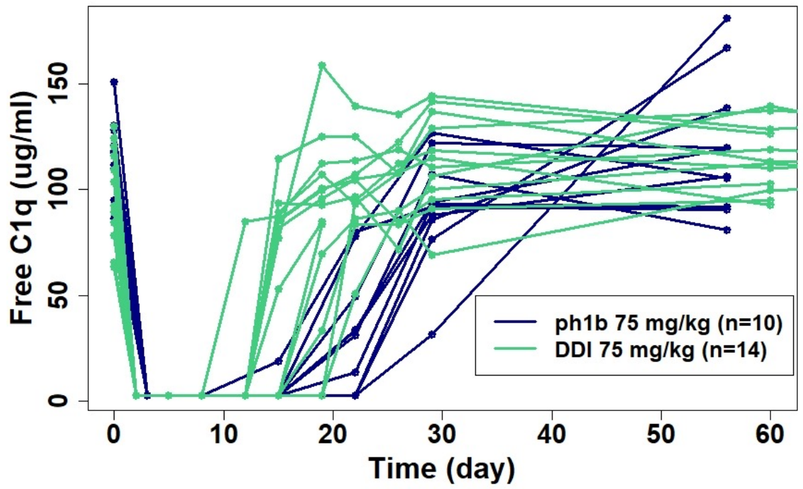
Achieved full C1q target engagement and duration of C1q suppression maintained within 1-3 weeks targeted window

Pharmacokinetics



- As anticipated, minimal reduction in exposure due to enhanced IgG clearance by IVIg
- Faster initial infusion rate in DDI than used in Phase 1b led to higher and earlier Cmax

Pharmacodynamics



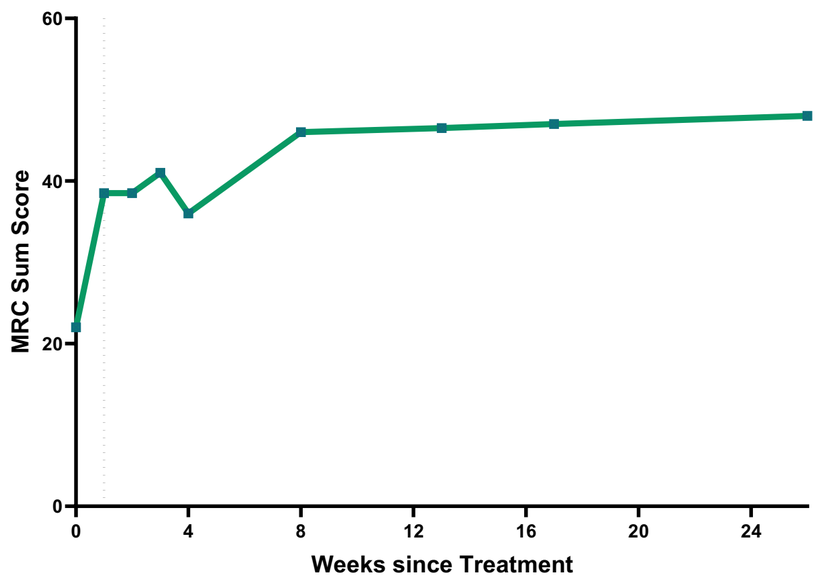
- Full target engagement in all subjects
- As anticipated, duration of complement inhibition reduced but maintained within
- target range of 1-3 weeks

Demographics and Baseline Characteristics

Bangladeshi subjects enrolled later and had more severe disease than Danish GBS subjects

PARAMETER	ALL	BANGLADESH	DENMARK
N	14	11	3
Age (mean, range)	41.1 (18-72)	33.3 (18-52)	54.7(28-72)
Male %	85.8%	90.1%	66.7%
Days from symptoms to treatment (mean, range)	**8.8 (3,13)**	**9.5 (6, 13)**	**6.7 (3, 9)**
Electrodiagnosis (D1 - Hadden)			
Axonal (AMAN)	**42.9%**	**45.5%**	**33.3%**
Demyelinating (AIDP)	50.0%	45.5%	66.7%
Equivocal or Other	7.2%	9.1%	0.0%
GBS-DS (mean)	4.0	4.1	3.7
# GBS-DS 3	3 (21.4%)	2 (18.2%)	1 (33.3%)
# GBS-DS 4	8 (57.1%)	6 (54.5%)	2 (66.7%)
# GBS-DS 5	3 (21.4%)	3 (27.3%)	0 (0.0%)
MRC sum score (mean, range)	**20.1 (0-42)**	**15.8 (0-38)**	**35.7 (32-42)**
Serum Neurofilament Light (mean, SD)	**1110.3 ±1144.1**	**1397.9 ±1077.4**	**55.7 ±32.9**

Early Improvement in Muscle Strength (MRC Sum Score) in DDI Trial



- Improvement in muscle strength (MRC sum score) observed within 1 week of initiation treatment
- MRC is most significant predictor of functional outcomes (mEGOS) in GBS[1]
- Improvement in MRC sum score precedes and drives the change in GBS-DS functional score

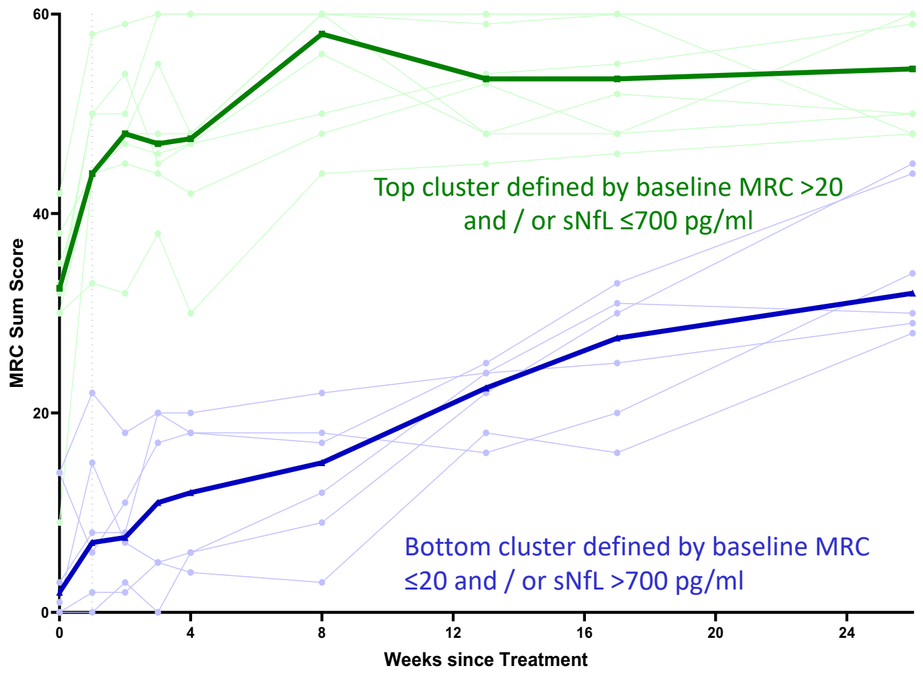
[1]*Walgaard, C., H. F. Lingsma, L. Ruts, P. A. van Doorn, E. W. Steyerberg, and B. C. Jacobs., Neurology 76(11):968–75*

Two Clusters of GBS Subjects Defined by Baseline Serum NfL and Muscle Strength with Different Trajectories to Functional Recovery

Top cluster consisting of Bangladeshi and Danish subjects have similar functional outcomes at Week 26

Pattern of change in function over time favors a longitudinal analysis of data in GBS

Muscle Strength over 26 Weeks



Cluster with early functional improvement and GBS-DS <3 at Wk26

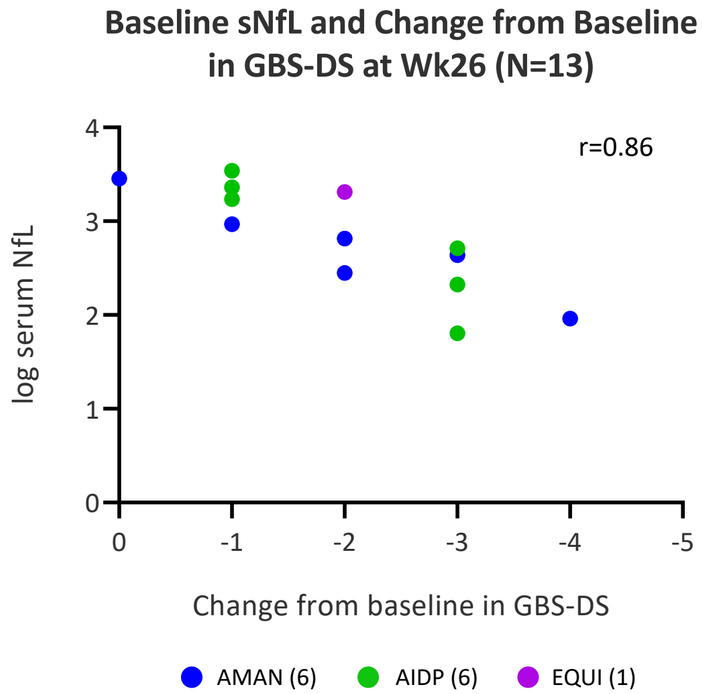
Baseline Parameters				GBS-DS Score over 26 weeks								
MRC	NfL	Origin	NCS	Wk 0	Wk 1	Wk 2	Wk 3	Wk 4	Wk 8	Wk 13	Wk 17	Wk 26
42	64		AIDP	3	2	2	1	1	1	1	1	0
35	516		AIDP	3	2	2	2	2	1	1	1	0
32	92		AMAN	4	3	2	2	2	1	2	1	0
30	435		AMAN	4	2	2	2	2	1	1	0	1
9	211		AIDP	4	3	2	1	1	2	1	1	1
38	281		AMAN	3	3	2	2	2	1	1	1	1
30	652		AMAN	4	4	4	3	4	3	2	2	2
33	12		AIDP	4	4	3	3	4	4	3	3	2

Cluster with later functional improvement and GBS-DS ≥3 at Wk26

MRC	NfL	Origin	NCS	Wk 0	Wk 1	Wk 2	Wk 3	Wk 4	Wk 8	Wk 13	Wk 17	Wk 26
14	1714		AIDP	4	4	4	4	4	4	4	4	3
3	3445		AIDP	4	4	4	4	4	4	4	3	3
0	2048		EQUI	5	5	5	5	5	4	4	4	3
14	2850		AMAN	4	4	4	4	4	4	4	4	4
0	928		AMAN	5	5	5	5	5	4	4	4	4
1	2298		AIDP	5	5	5	5	4	4	4	4	4

Initial improvement in GBS-DS Treatment Related Fluctuation

Preliminary Results: Serum NfL Important Prognostic Biomarker



- Baseline serum neurofilament light (sNfL) was elevated in all subjects (range 64-3445 pg/ml)
  - NfL levels are presented log transformed
- Serum NfL correlated closely with clinical outcome (GBS-DS) over 26 weeks (Spearman, r=0.86, p=0.0004)
- In all neurotypes baseline serum NfL was indicative of outcome
- Serum NfL was a prognostic biomarker in both Bangladesh and Denmark
- A reduction in sNfL was observed after treatment in the majority of subjects

Summary

- IVIg-ANX005 combination well-tolerated with no change to safety profile of either IVIg or ANX005
- Full C1q target engagement was observed in all subjects
- C1q suppression was maintained within the 1-3 weeks targeted range of complement inhibition
- Baseline MRC sum score and serum NfL defined 2 clusters representing subjects' trajectories to final functional status
- Baseline serum NfL is an important and independent prognostic biomarker
- Considering baseline MRC sum score and / or serum NfL, subjects from Bangladesh and Denmark had similar outcomes
- A longitudinal proportional odds efficacy analysis that summarizes subjects' trajectories over time is proposed for future GBS studies
- A placebo-controlled Phase 2/3 study is ongoing to evaluate the efficacy of ANX005 monotherapy in improving disability in subjects with GBS