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Breaking New Ground In The Treatment Of Guillain-Barré Syndrome

Tuesday, 25th June

Peripheral Nerve Society, 2024 Annual Meeting

Montréal, Québec, Canada

Disclosures

- Consultant: Annexon Biosciences, AstralBio, Avilar Therapeutics, Boehringer Ingelheim, Dianthus Therapeutics, Grifols S.A., Immunovant, Johnson & Johnson, Longboard Pharmaceuticals, Novartis, Nuvig Pharma, Octapharma AG, Seattle Genetics Inc.
- Data Safety Monitoring Board: Avidity Bio, PledPharma AB, Hansa Medical AB, Mitsubishi Tanabe Pharma Corporation, Passage Bio, Sanofi, Vertex
- Technology Licensing: Worldwide Clinical Trials, Inc., Beijing 3E-Regenacy Pharmaceuticals Co., Ltd., Passage Bio, CMIC, MedImmune Ltd., Fundacion GELTAMO, RWS Life Sciences
- SAB: Algotherapeutics, Nervosave

Topline Results of the Phase 3 Trial of ANX005 in patients with Guillain-Barré Syndrome will be presented at the Hughes Clinical Highlights Session

Symposium Goals and Objectives

1. Address the risk of GBS as a serious life-threatening neurological emergency that requires early diagnosis and targeted treatment

2. Review the role of classical complement activity as a key mediator of nerve fiber damage and nerve fiber repair in GBS

3. Present data on the potential role of inhibiting C1q to improve the overall health status of patients with GBS

Opportunities for Advancements in Treating GBS

Treatment for GBS has not changed in the last 30 years

1 **Targeted immunotherapy approaches to prevent extensive nerve damage**

Treatment goal is to target complement-mediated acute nerve damage and inflammation to prevent paralysis, severe morbidity, disability and mortality

2 **Rapid administration and onset of action**

Block acute and ongoing destruction of nerves immediately

3 **Clinical benefit across entire disease spectrum**

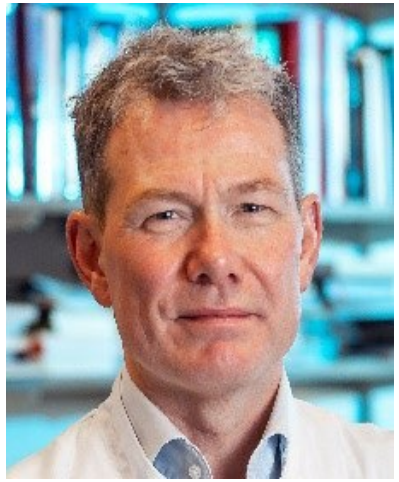
Effective in all GBS patients, and impacting all aspects of the disease that are important to patients

4 **Minimal side-effects**

Single infusion with manageable infusion related reactions

Symposium Faculty

David R. Cornblath, MD
Professor Emeritus
John Hopkins University
Medical Center



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Executive Director
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Symposium Agenda

Breaking New Ground In The Treatment Of Guillain-Barré Syndrome		
Time	**Topic**	**Speaker**
13:15 PM	Welcome & Introduction	David R. Cornblath, MD
13:25 PM	GBS Revisited	Bart Jacobs, MD
13:35 PM	Role of Complement & Biomarkers in GBS Pathogenesis	Luis Querol, MD, PhD
13:45 PM	GBS Treatment: Can We Do Better?	Jeff Allen, MD
14:00 PM	Panel Discussion	David R. Cornblath, MD
14:15 PM	Closing	David R. Cornblath, MD

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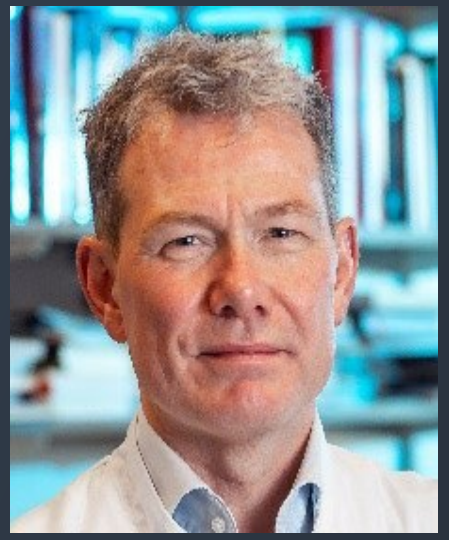
Guillain-Barré Syndrome Revisited



Bart C. Jacobs, MD, PhD

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Disclosures

Sponsoring for scientific research projects:

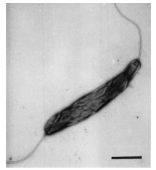
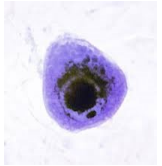
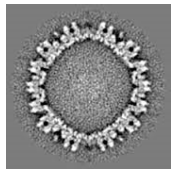
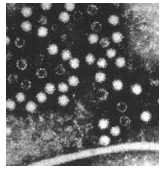
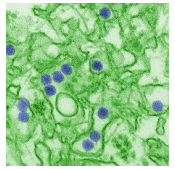
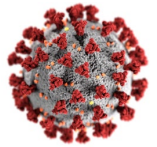
- EU Horizon 2020 (ZikaPLAN)
- NWO and ZonMW
- Spierfonds (Prinses Beatrix Spierfonds, Spieren voor Spieren)
- GBS-CIDP Foundation International (IGOS)
- Grifols (eSPIN Award, I-SID trial)
- CSL-Behring (ICOS, Interlaken Leadership Award)
- Hansa Biopharma
- Roche
- Annexon Biosciences

Presentation Objectives

- Understand how GBS is a neurological emergency with significant long-term residual morbidity
- Recognize that GBS subtypes do not have a role in clinical management
- Convey the importance for treating GBS with a targeted intervention

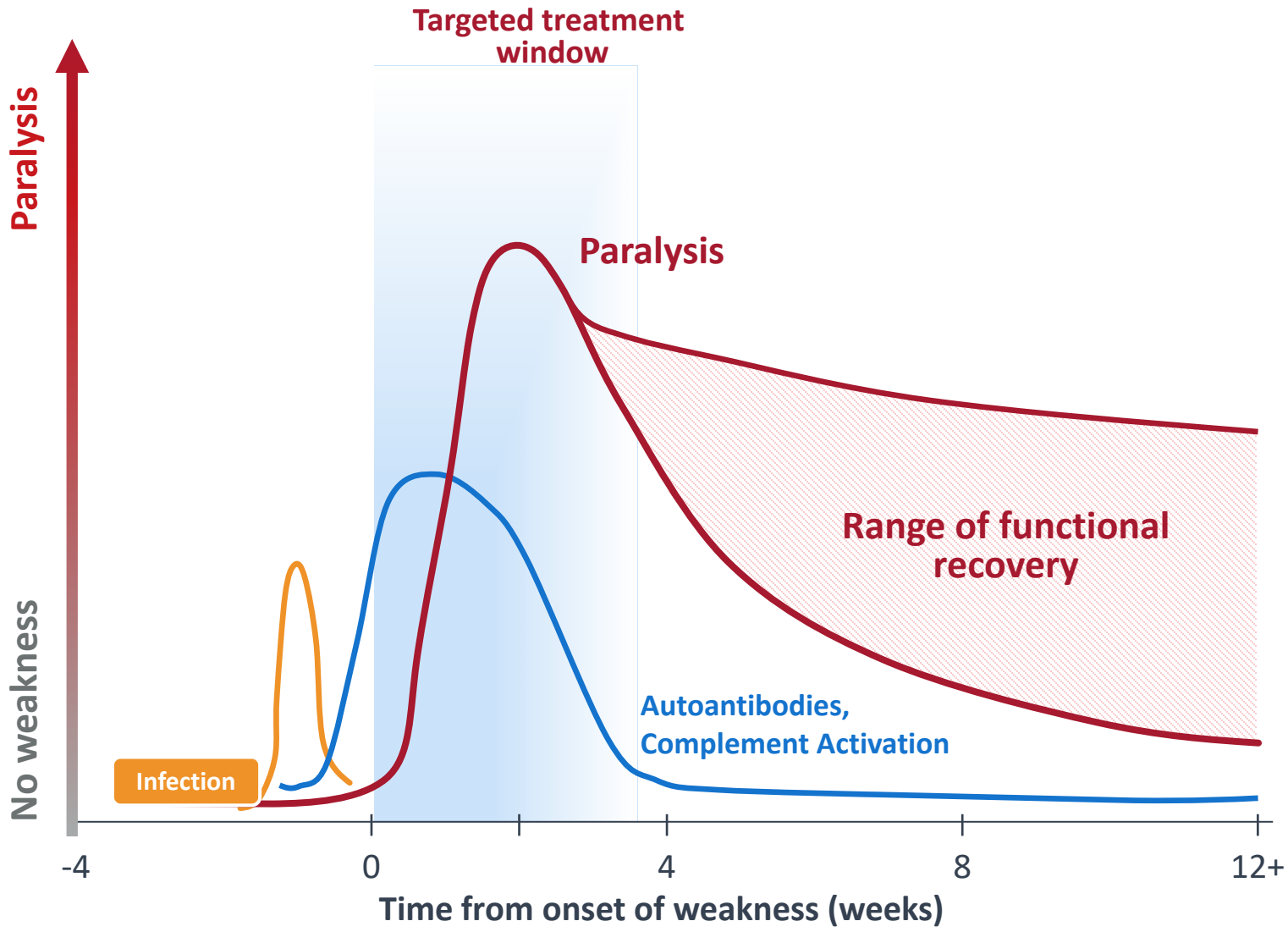
Impact of GBS: A Neurological Emergency

- Predominant form of acute flaccid symmetrical paralysis
- Worldwide incidence 150,000 patients per year
- Immune-mediated polyradiculoneuropathy, usually post-infectious

Campylobacter jejuni	Cytomegalo virus	Epstein-Barr virus	Hepatitis E virus	*Mycoplasma pneumoniae*	Zika virus	SARS-CoV-2 virus
						
30%	4%	1%	3%	10%	variable	rare

- Usually sporadic, but also in outbreaks due to infections
- Neurological emergency
  - 20% develop respiratory failure requiring ventilation
  - 10% develop severe autonomic dysfunction
  - Mortality rate 2-5% (or higher)

Targeted Treatment Given Early Could Maximize Outcome



1. van den Berg B et al. *Nat Rev Neurol*. 2014;10(8):469-482. 2. Leonhard SE et al. *Nat Rev Neurol*. 2019;15(11):671-683.

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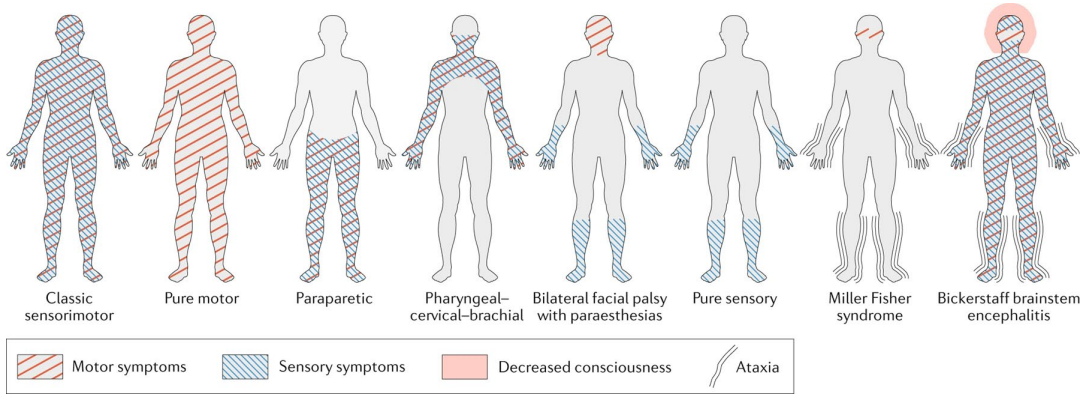
GBS Requires Rapid Diagnosis and Management

- Early diagnosis can be challenging
  - Differential diagnosis and rarity and variability of GBS



- Current treatments with IVIg or PE frequently insufficient
  - Disease progression in 20-30%
  - Treatment-related fluctuations 15%
  - Prolonged and incomplete recovery

- An ideal treatment would rapidly and completely stop antibody/complement-driven nerve injury

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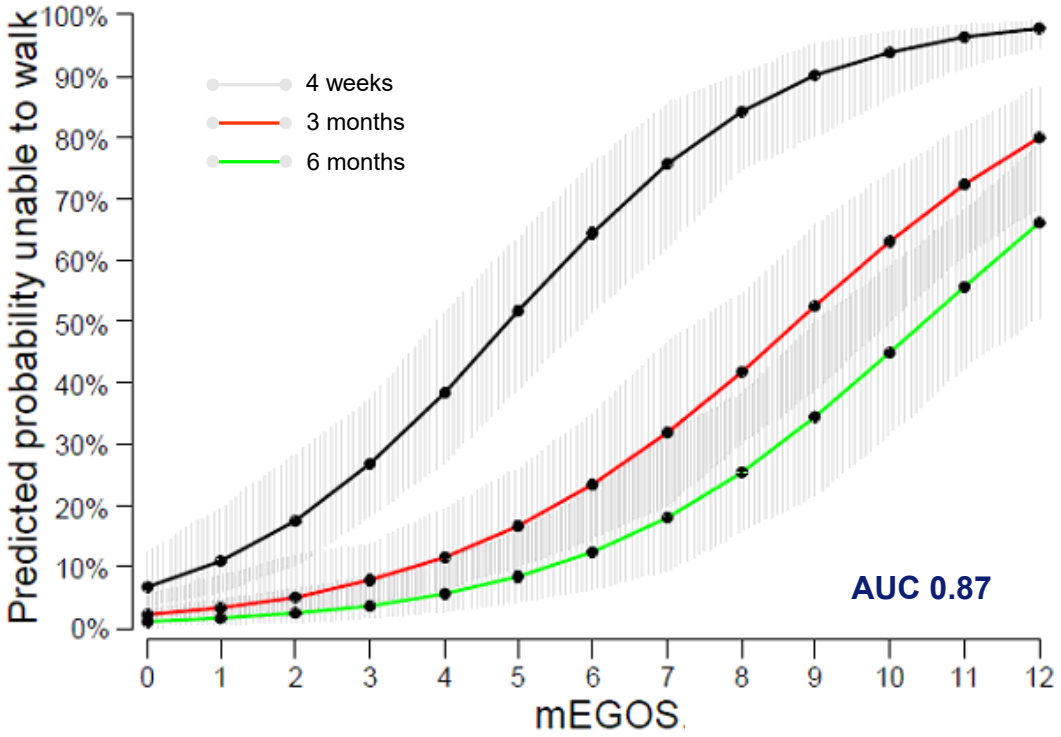
Prediction of Recovery in GBS is Mainly Driven by MRC Sumscore

Modified Erasmus GBS outcome score (mEGOS)

Predictors	Categories	Score
Age (years)	≤40	0
	41 - 60	1
	>60	2
Diarrhoea (≤ 4 weeks)	absent	0
	present	1
MRC sumscore (at 1 week)	51 - 60	0
	41 - 50	3
	31 - 40	6
	0 - 30	9
mEGOS.7		**0 - 12**

Chance unable to walk at 4 weeks, 3 and 6 months according to mEGOS (N=555)



Additional studies

Validation studies

- Japan (Yamagishi 2017)
- Malaysia (Tan, 2019)
- IGOS (Doets, 2022)
- Bangladesh (Papri 2022)

Prognostic Biomarkers

- Infections
- Antibodies
- NCS (ulnar CMAP)
- NfL
- others

Walgaard et al., Neurology 2011

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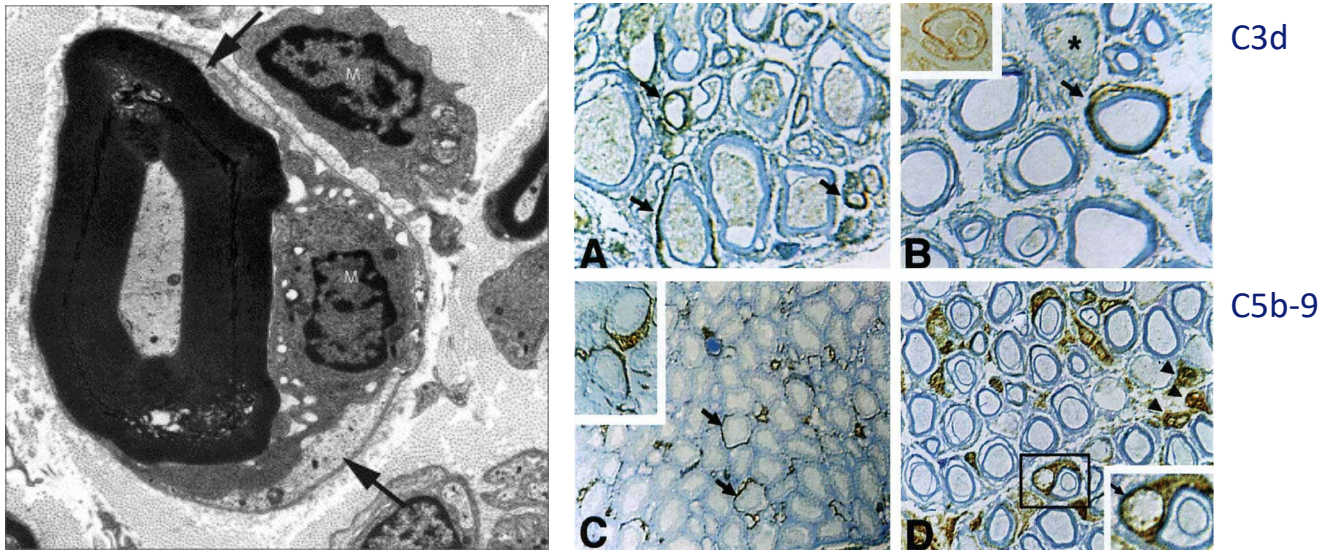
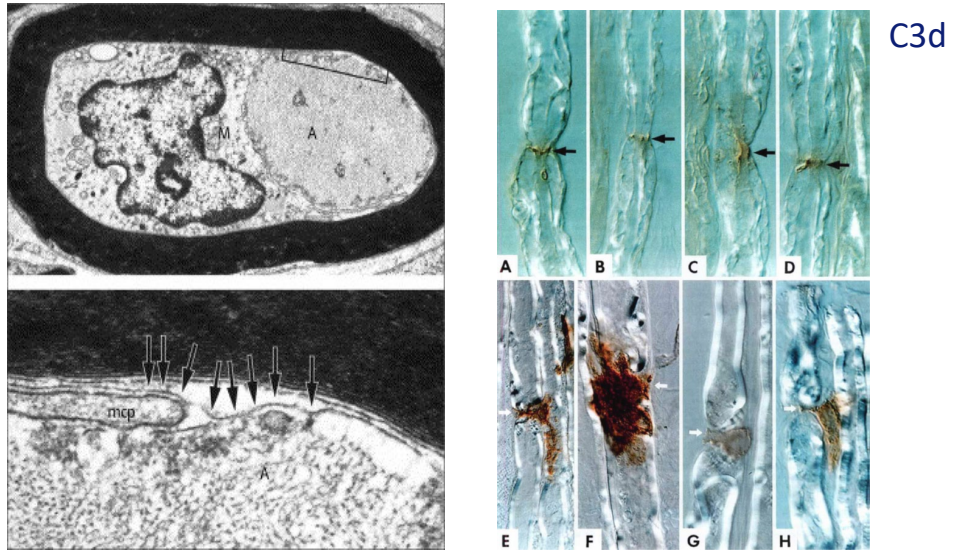
The Role of Complement in GBS Subtypes

Complement is activated by autoantibodies on axon and myelin

Acute Inflammatory Demyelinating Polyneuropathy (AIDP)



Acute Motor Axonal Neuropathy (AMAN)



Griffin et al. Ann Neurol 1994, Hafer-Macko et al. Ann Neurol 1997

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What is the Relevance of GBS Subtypes for Treatment?

- Histopathology rarely available
- Nerve conduction studies
  - Various sets of criteria in use
  - Frequently equivocal subtype
  - Subtype classification may change over time
- Complement involved in all subtypes
- Treatment is the same
- Limited independent prognostic value

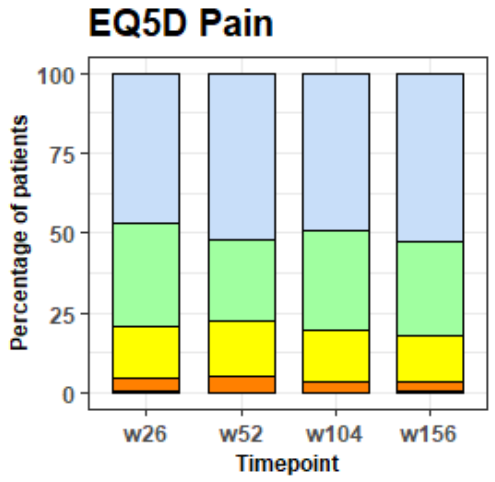
GBS is Associated with Significant Morbidity Even After 3 Years

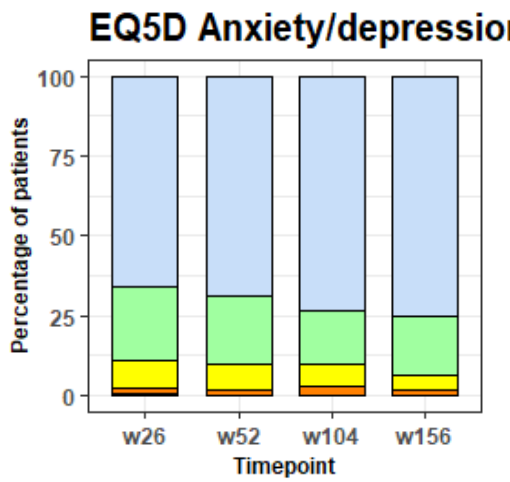
Quality of life (QoL) after diagnosis in patients from US/Europe*

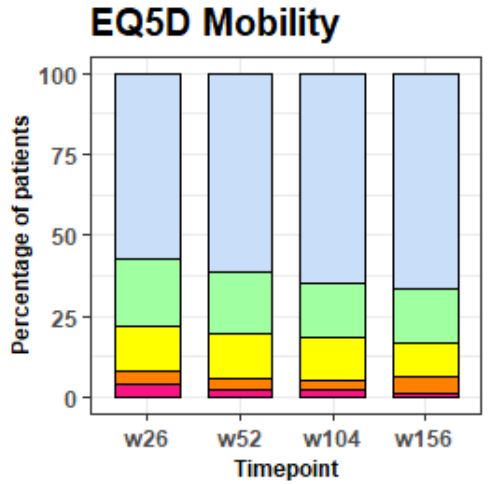
~50% have pain

~25% have depressive symptoms

~35% have impaired mobility







IGOS

*IGOS (N=1275) (unpublished data)

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Conclusions

- GBS is a rapidly progressive neurological emergency that requires early diagnosis and treatment
- Current treatments do not prevent severe residual effects in many patients
- Complement inhibition is an attractive therapeutic target in all GBS subtypes

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Role of Complement & Biomarkers in GBS Pathogenesis

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Barcelona, Spain

Disclosures

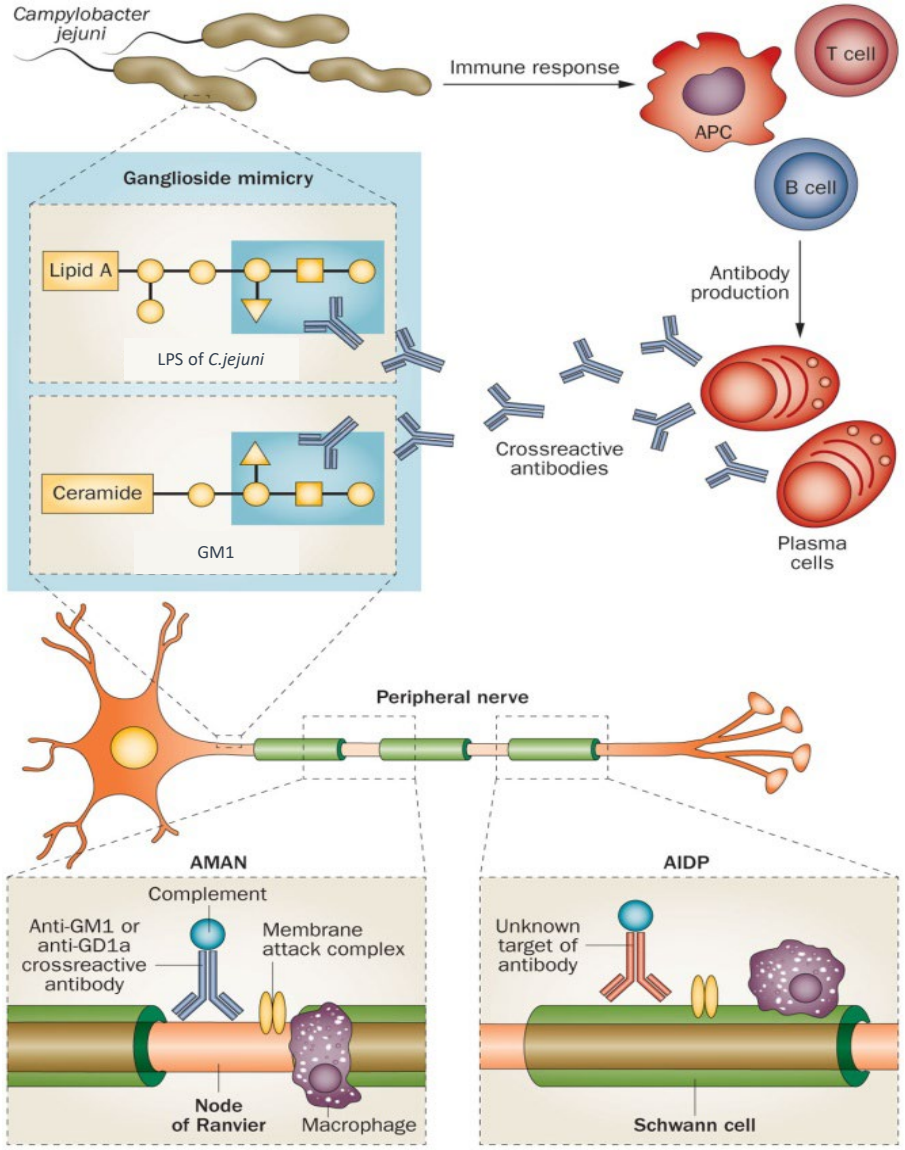
- LQ received research grants from Instituto de Salud Carlos III – Ministry of Economy and Innovation (Spain), CIBERER, Fundació La Marató, GBS-CIDP Foundation International, UCB, ArgenX and Grifols
- LQ received speaker or expert testimony honoraria from CSL Behring, Novartis, Sanofi-Genzyme, Merck, Annexon, Alnylam, Janssen, ArgenX, UCB, Dianthus, LFB, Avilar Therapeutics, Nuvig Therapeutics, Takeda and Roche
- LQ serves at Clinical Trial Steering Committees for Sanofi Genzyme, Takeda and ArgenX, and was Principal Investigator for UCB's CIDP01 trial.

Presentation Objectives

- Review the role of triggers and autoantibodies in GBS pathogenesis
- Discuss the importance of humoral immunity and upstream classical complement in neuroinflammation in GBS
- Address the role of biomarkers and neurotypes in GBS prognosis

Immunopathogenesis of GBS: Molecular Mimicry and Antiganglioside Antibodies

Autoantibodies are the humoral factor linking trigger and nerve damage in GBS

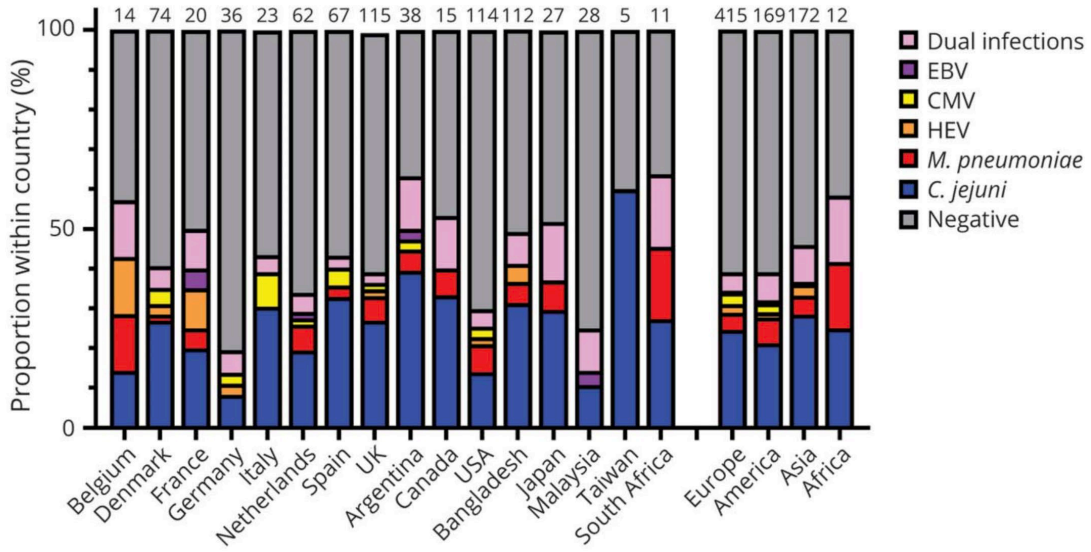


Van den Berg, B. *et al.* (2014) Guillain–Barré syndrome: pathogenesis, diagnosis, treatment and prognosis *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2014.121

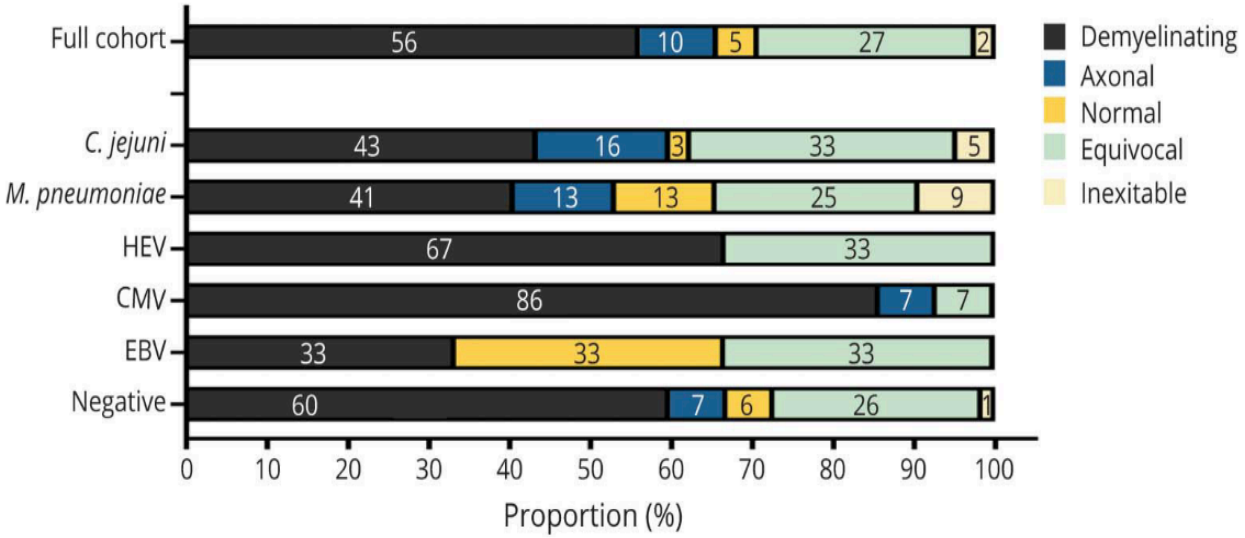
Campylobacter is the Most Prevalent Preceding Infection in GBS

No Clear Association Between Infection and GBS Neurotype

Preceding Infections by Country and Continent (%)



Electrophysiological Subtype by Infection Serology



Leonhard et al. JPNS 2021

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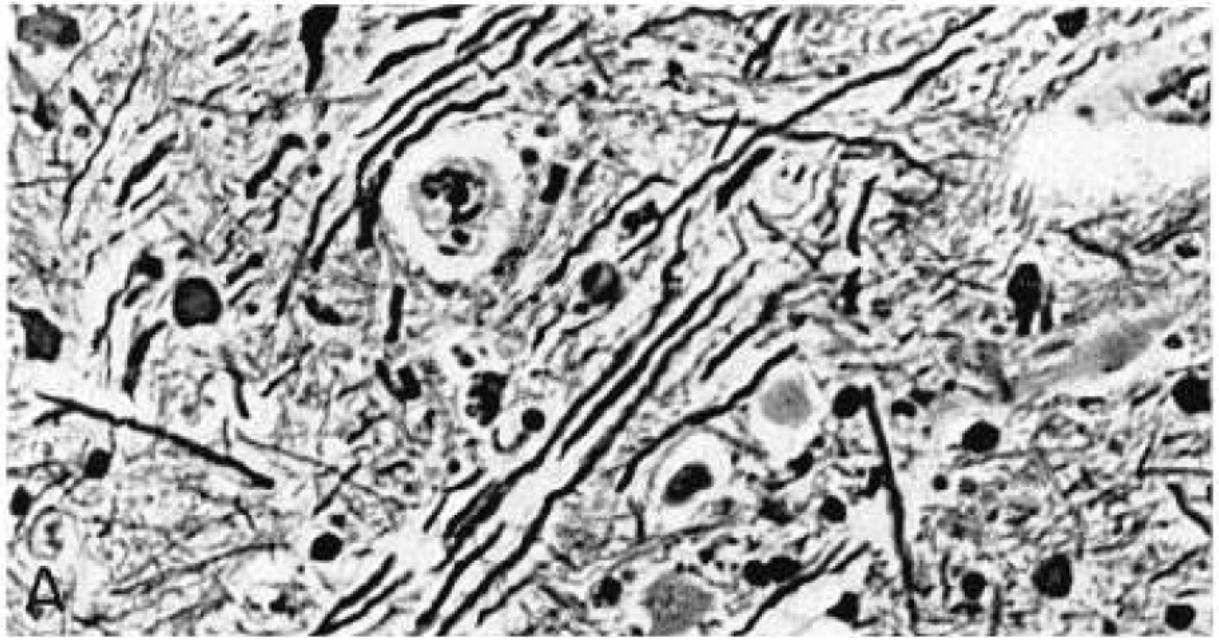
Oedema Precedes Cellular Infiltration in GBS Course

Ventral root: swelling, myelin, and axonal damage



Ventral root: Inflammatory Oedema

Haymaker and Kernohan, Medicine 1949; Berciano, Clin Neurol Neurosurg 2024

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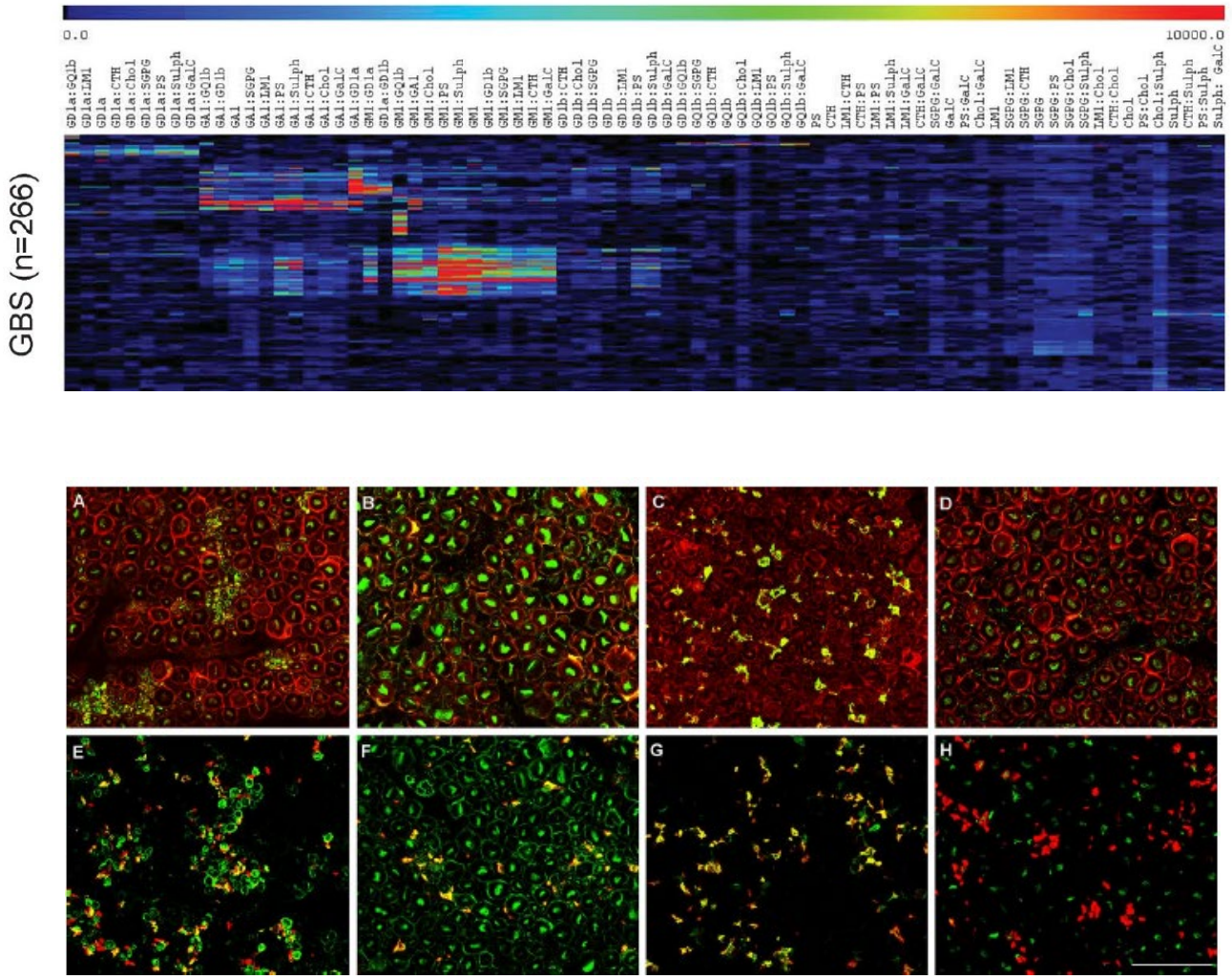
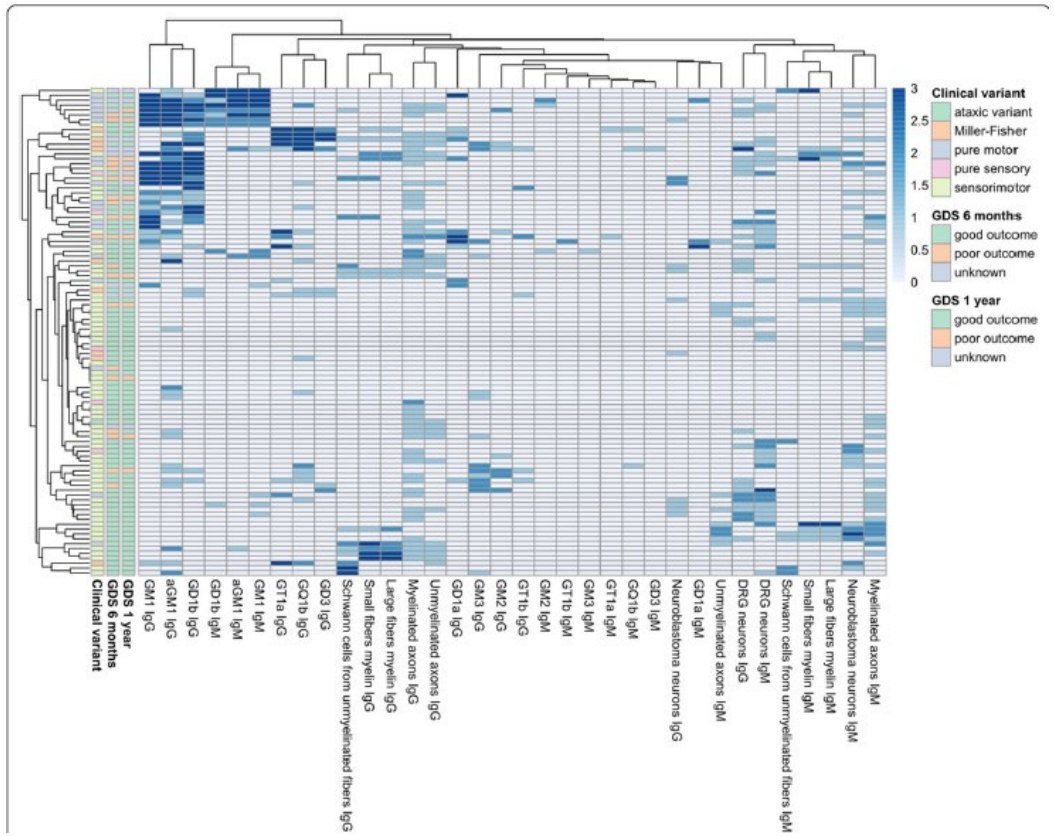
Autoantibodies Targeting Nerves are Common in GBS Across Subtypes





1.Halstead et al, Neurol NeuroImm Neuroinflamm 2016; 2.Lleixà et al, J Neuroinflamm 2021

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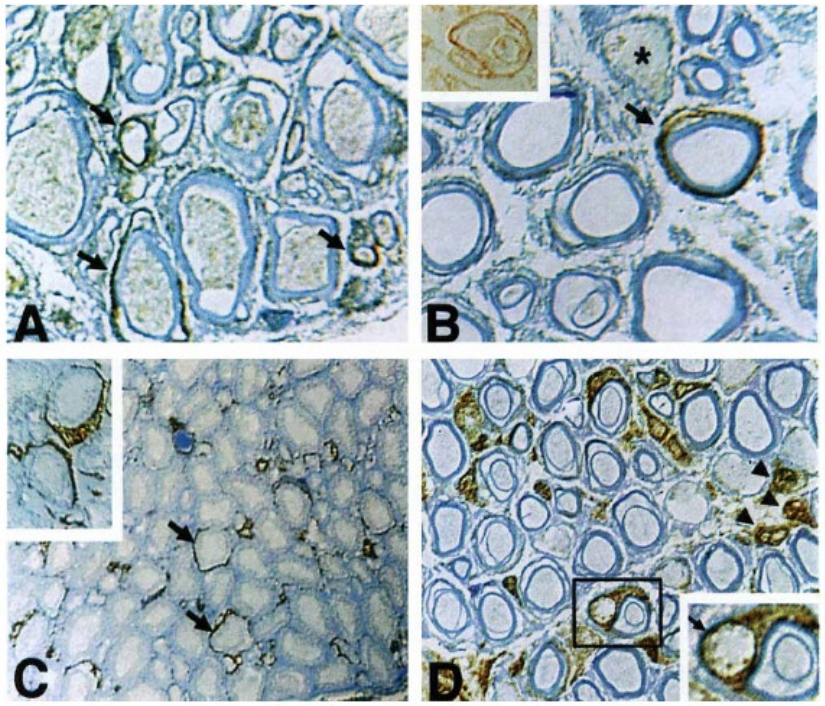
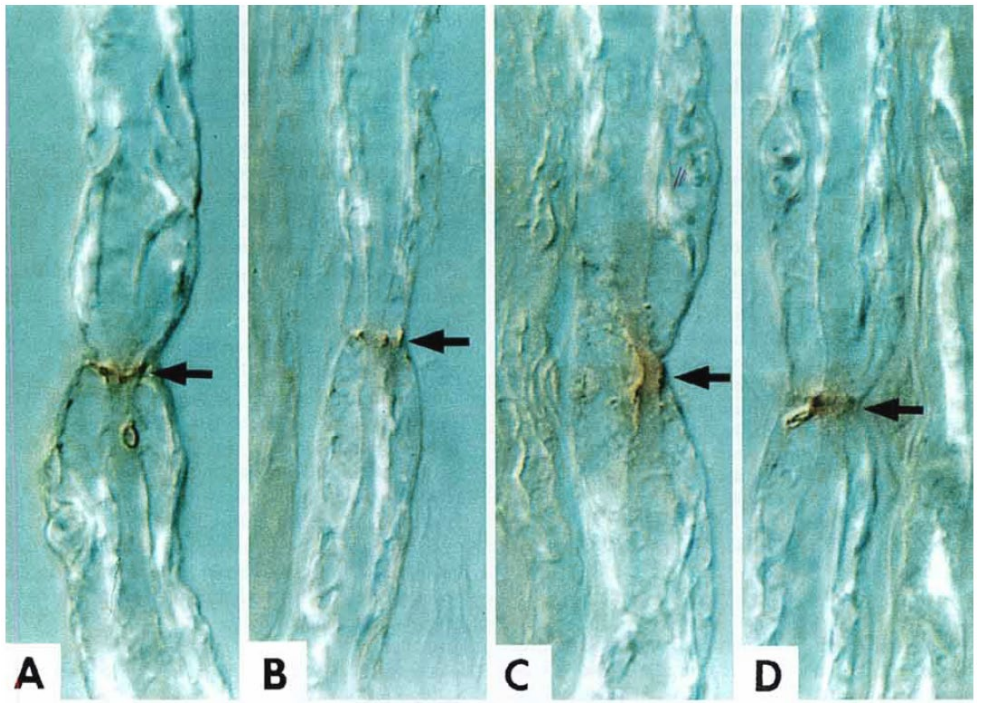
Antibody-Mediated Complement Activation Occurs Both on Myelin and Axons

Myelin



Node of Ranvier



Hafer-Macko, Ann Neurol 1996a; 2.Hafer-Macko, Ann Neurol 1996b

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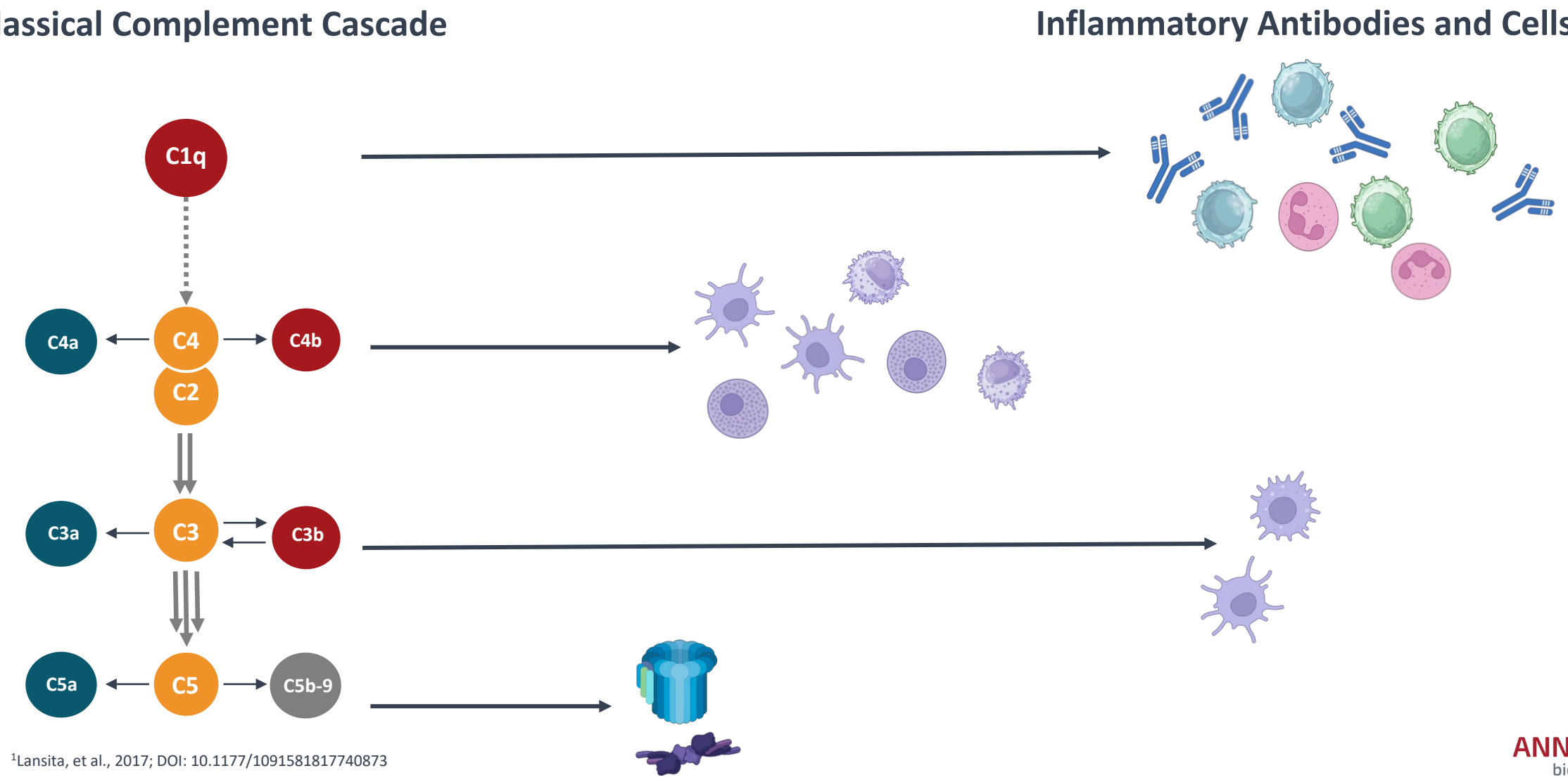
C1q Drives Harmful Neuroinflammation and Extensive Damage to Peripheral Nerve Fibers in GBS

C1q Inhibition Blocks Essential Effector Cells' Function Upstream



[1]Lansita, et al., 2017; DOI: 10.1177/1091581817740873

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Complement Inhibition Stopped Nerve Damage During Acute Autoimmune Injury while Inhibition During Recovery Phase Slowed Repair in Rat Models

Complement inhibition blocks acute nerve damage in an autoimmune neuropathy model

- Animals developed autoantibodies that activated complement and damaged peripheral nerves
- Acute damage blocked by complement inhibition

Complement Inhibition Protects Against Acute Nerve Damage in Autoimmune Neuritis

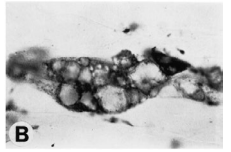
Complement inhibition during recovery phase slowed debris clearance and repair in an acute nerve injury model

- Wallerian degeneration with macrophage infiltration, myelin removal and axonal regrowth

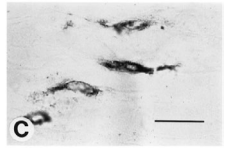
Clearance and Regrowth Slowed by Complement Inhibition

Debris Clearance by Macrophage **Axonal Repair**

Macrophage engorged with myelin debris

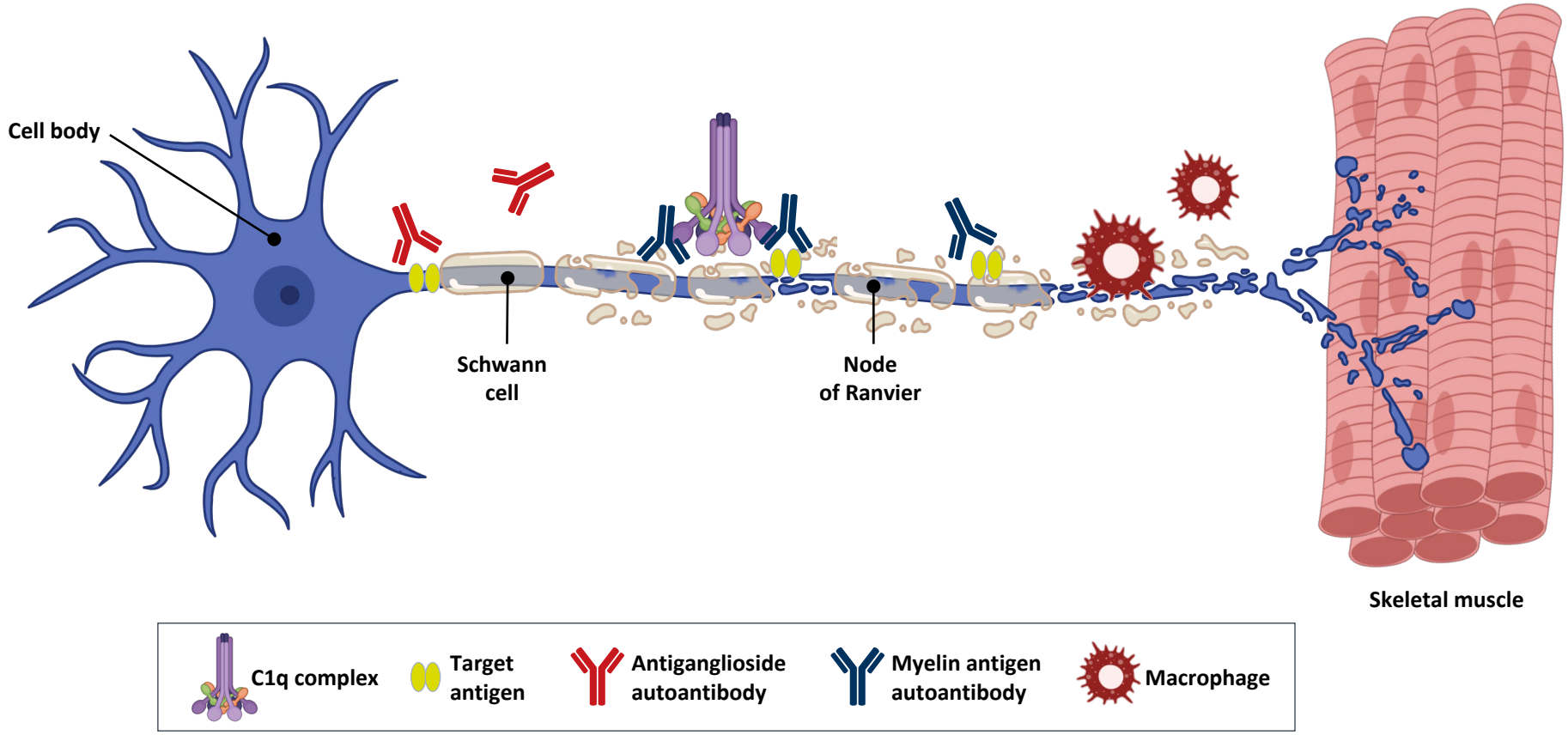


Resting macrophages w/ complement inhibition (cobra venom factor)



C1q Mediates Neuroinflammatory Axonal and Myelin Damage

C1q binds to IgG & IgM antibodies on nerve, activates classical complement pathway



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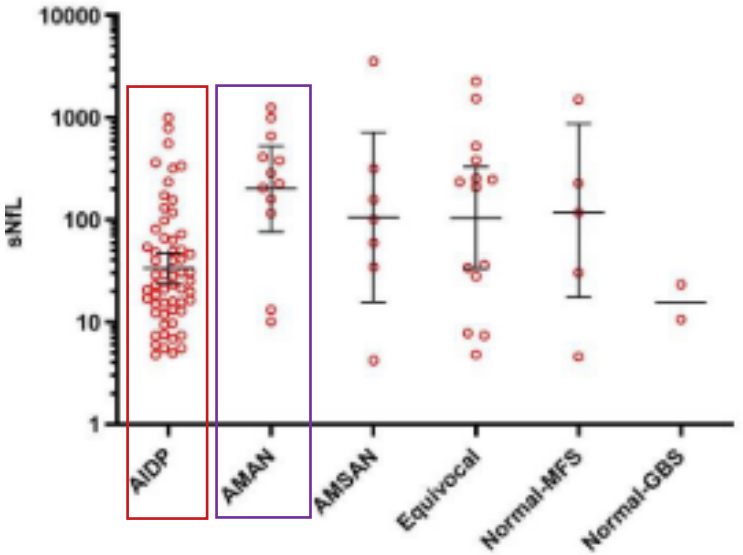
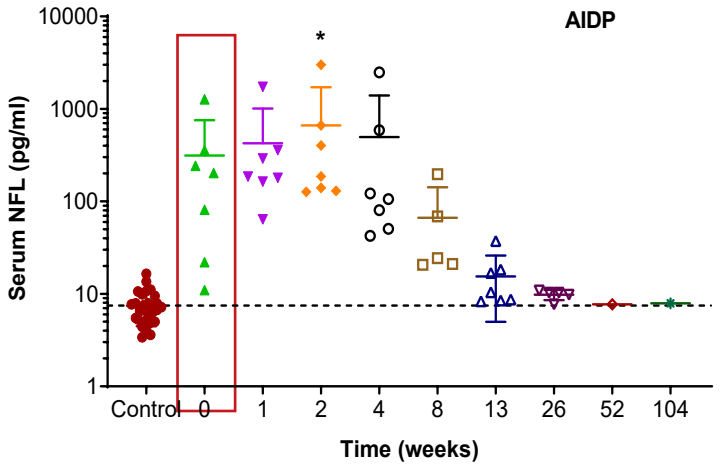
Elevated NfL Levels Indicate Axonal Damage

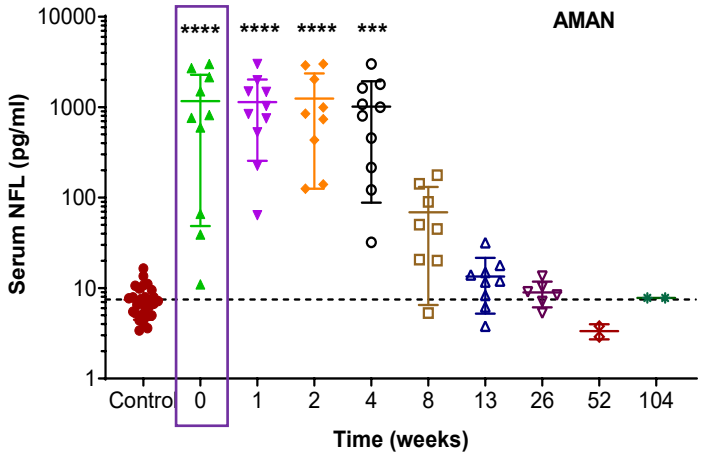
Magnitude of NfL elevations, an indicator of axonal damage, is prognostic and a marker of severity

IGOS Spain

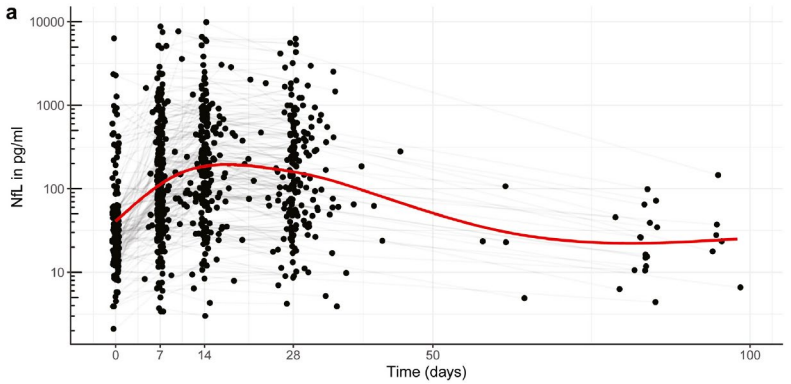


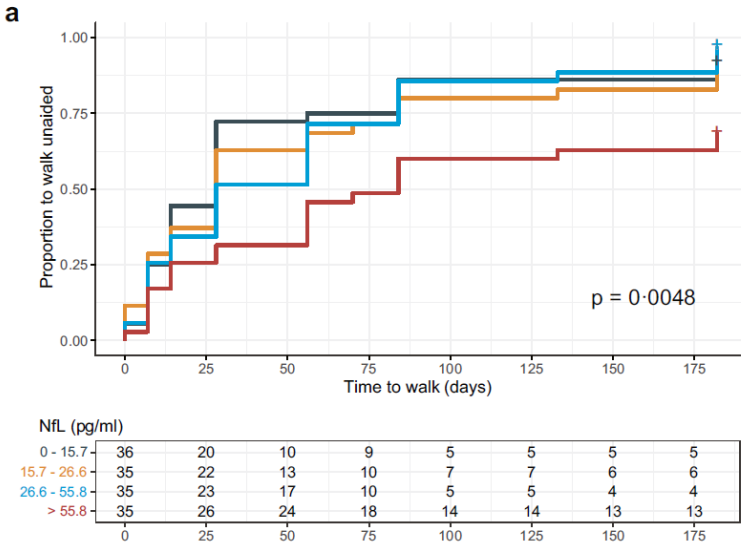
IGOS Bangladesh





IGOS Netherlands





1.van Tilburg, et al. eBioMedicine 2024;102: 105072 doi.org/10.1016/j.ebiom.2024.105072; 2.*Martín-Aguilar L, Camps-Renom P, Lleixà C, et al. medRxiv. 2020:2020.03.24.20042200. doi:10.1101/2020.03.24.20042200;*
3.Collaboration with Badrul Islam, Zhahirul Islam (ICDDR, Bangladesh) and Deen Mohammed (Dhaka Medical College and Hospital); 4.Annexon data on file

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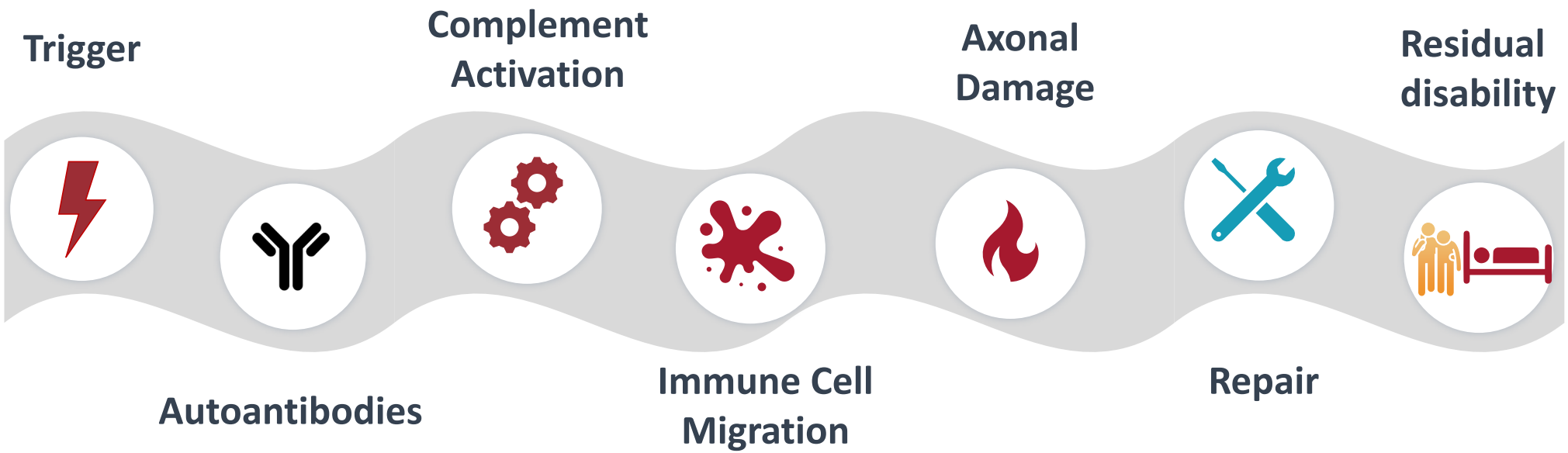
Characterizing the Course of GBS



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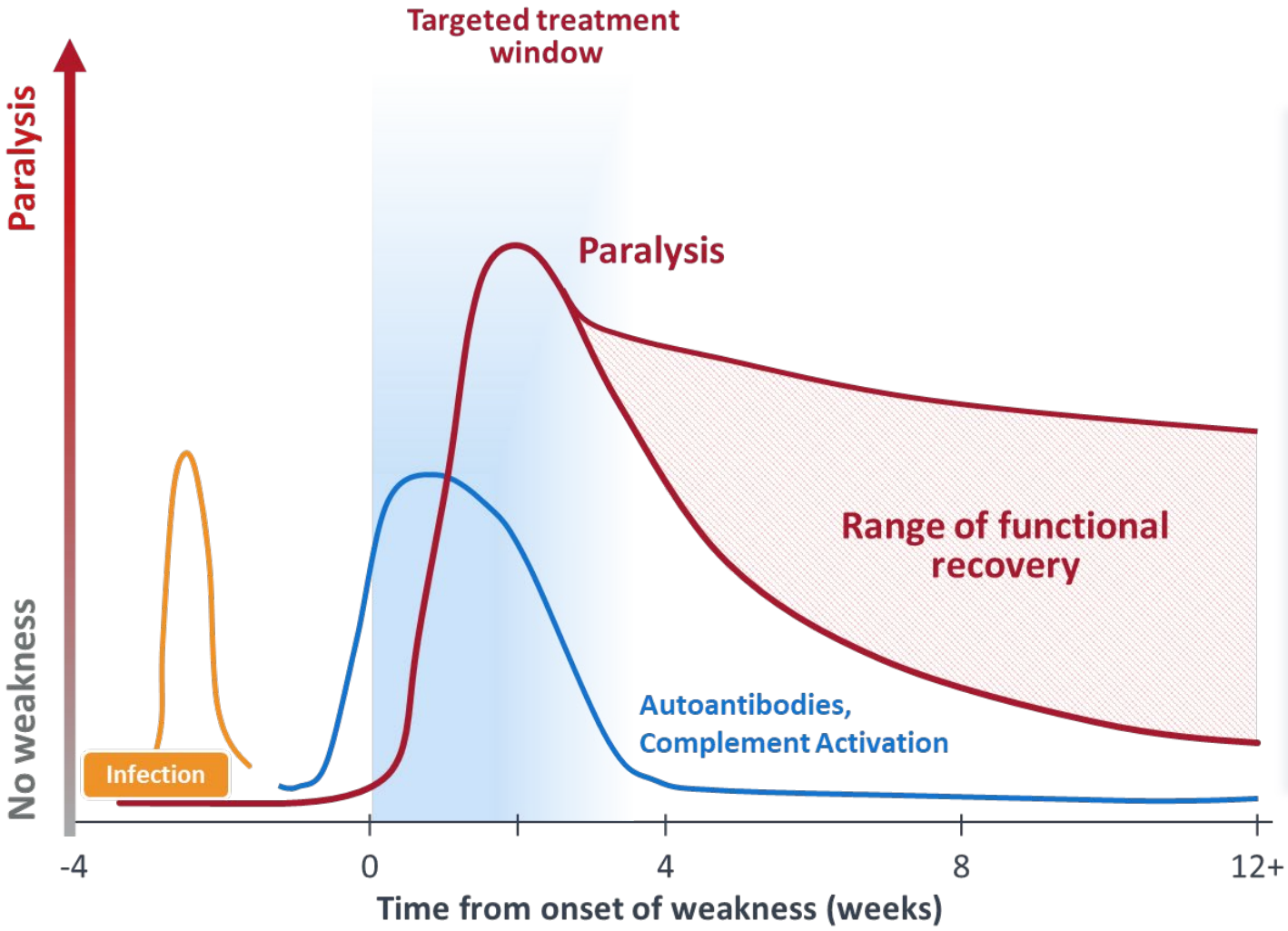
Complement Inhibition During the Active Disease Phase is Key

Acute disease phase of GBS is generally short and varies by patient



- GBS has an acute disease phase followed by spontaneous recovery
- Objectives of anti-C1q treatment in GBS
  - ✓ <u>Block</u> complement-mediated nerve damage during the acute disease
  - × <u>Do not block</u> complement-facilitated nerve repair during recovery phase
- Target treatment window is likely within first 2 weeks

1. van den Berg B et al. *Nat Rev Neurol*. 2014;10(8):469-482. 2. Leonhard SE et al. *Nat Rev Neurol*. 2019;15(11):671-683.

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The Treatment of Guillain-Barré Syndrome: Can we do better?

Jeff A. Allen, MD

Professor of Neurology

University of Minnesota

Disclosures

- Jeff Allen is a consultant for Alexion, Annexon, Alnylym, AstraZeneca, Argenx, Octaphama, CSL Behring, Takeda, Pfizer, Immunopharma, Immunovant, Grifols, Sanofi, and Jonson & Johnson.

Presentation Objectives

- Review current standards of care in GBS
- Address key characteristics of optimal GBS treatment
- Outline key characteristics of ANX005 Ph1b and pivotal Ph3 study
- Patients with GBS can **G**et **B**etter **S**ooner

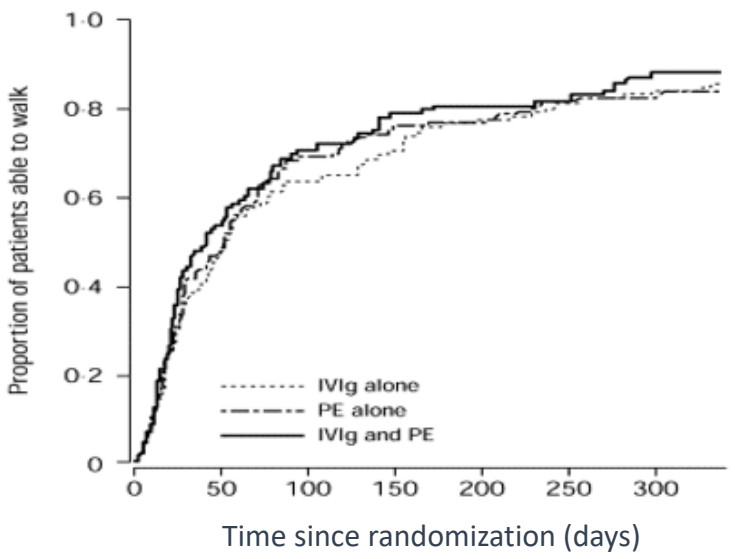
Current GBS Treatments: What do we know?

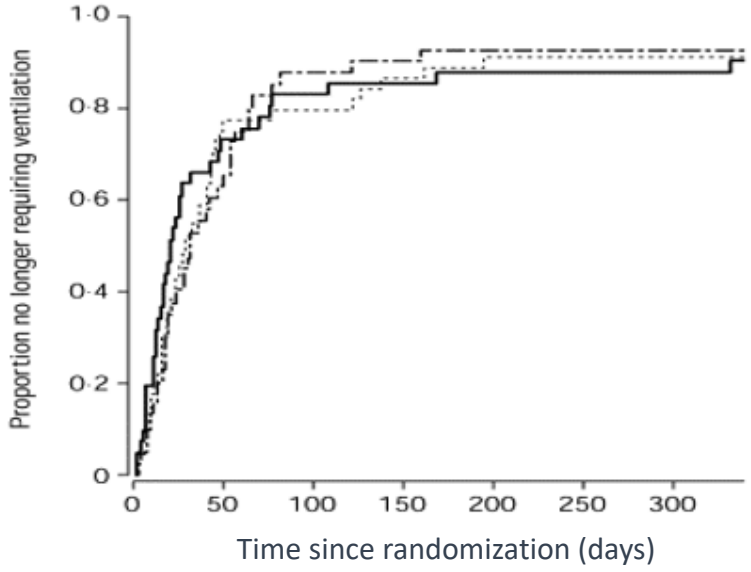
1. Plasma exchange and IVIg impact recovery
2. Sooner treatment is better than later treatment
3. Unknown if IVIg and PE impact the long-term outcome
4. Some IVIg or PE is important, but more is not always better
5. No IVIg placebo-controlled trials

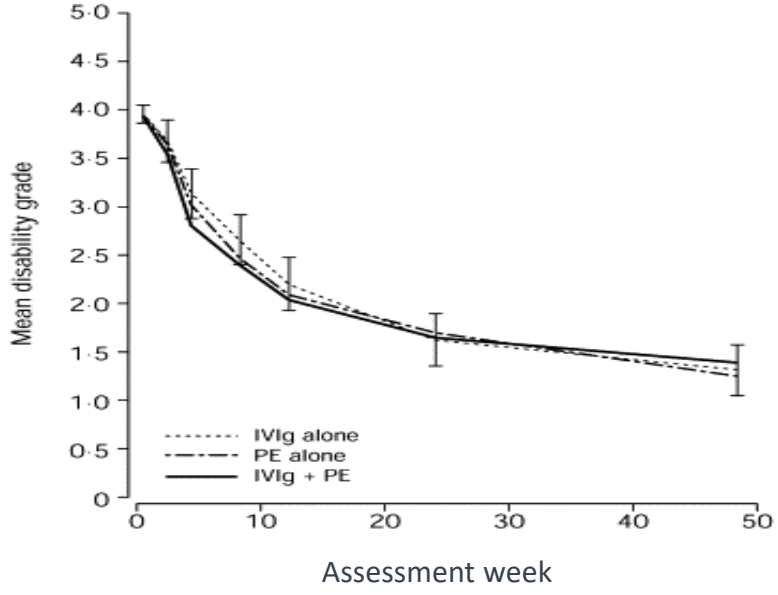
Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome. Lancet 1997

Current GBS Treatment: IVIg and PE Appear to be Equally Effective

No placebo-controlled IVIg trials







Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome. Lancet 1997

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IVIG: Some is Important…

SID-GBS study evaluated 2nd IVIg dose in patients with GBS with poor prognosis

Key Study Outcomes

- **No improvement in disability** at week 4 in re-treated group
- **More SAEs** (35% vs 16%) in re-treated group
  - Including thromboembolic events
  - N=4 died in the intervention group

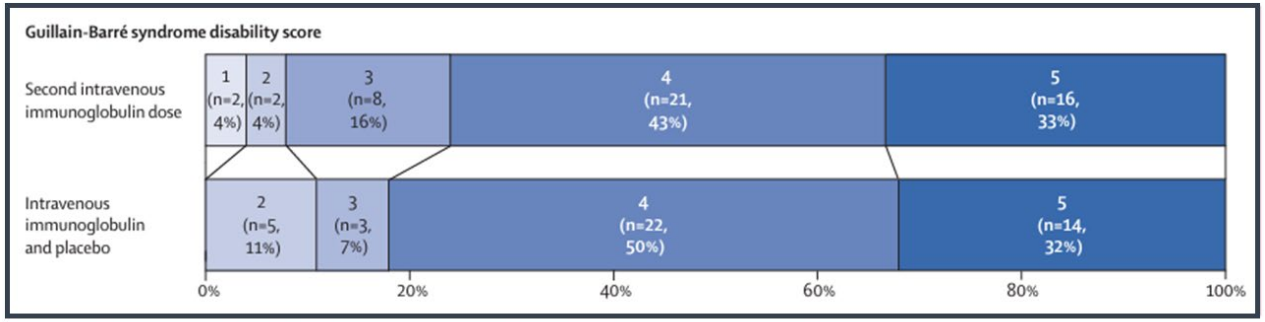

Figure 2: Guillain-Barré syndrome disability score at 4 weeks in the modified intention-to-treat population

…but more is not always better

Walgaard C et al. Second intravenous immunoglobulin dose in patients with Guillain-Barré syndrome with poor prognosis (SID-GBS): a double-blind, randomised, placebo-controlled trial. Lancet Neurology 2021.

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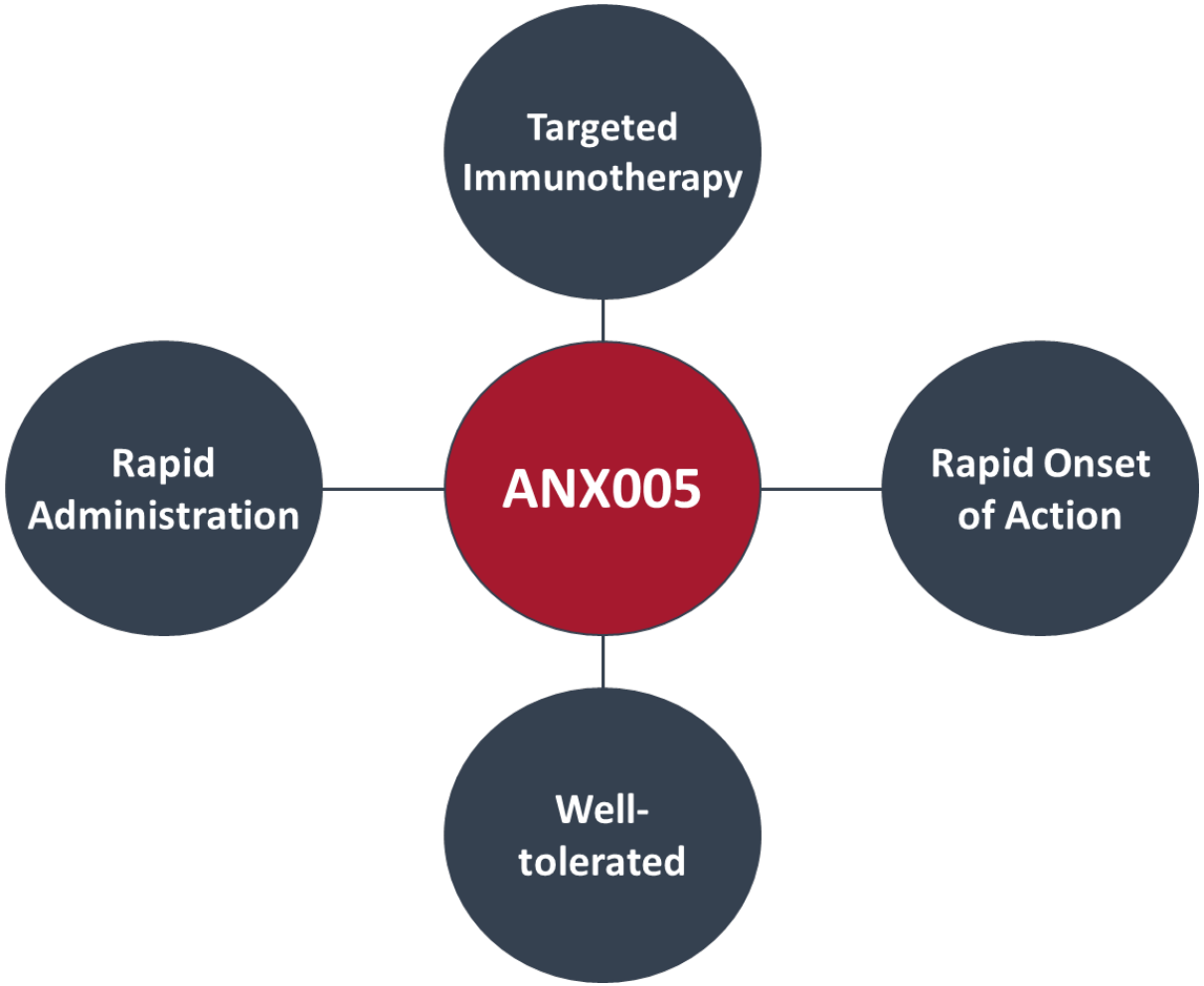
ANX005 has the Characteristics Required to Treat GBS



ANX005

- Humanized monoclonal antibody
- Rapidly inhibits C1q and the entire classical complement pathway
- Single infusion in GBS

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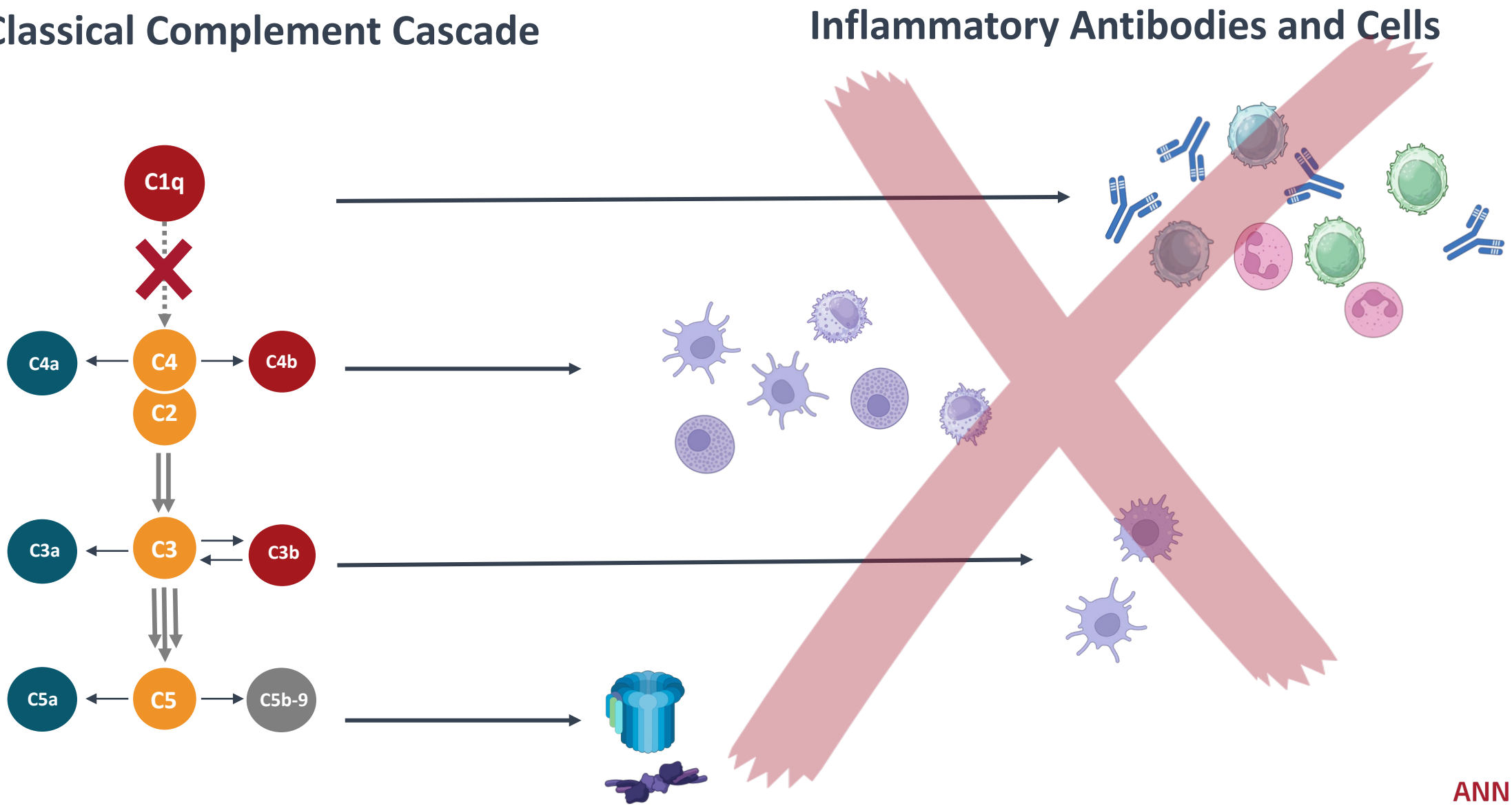
C1q Inhibition Blocks Harmful Neuroinflammation and Extensive Damage to Peripheral Nerve Fibers in GBS



[1]Lansita, et al., 2017; DOI: 10.1177/1091581817740873

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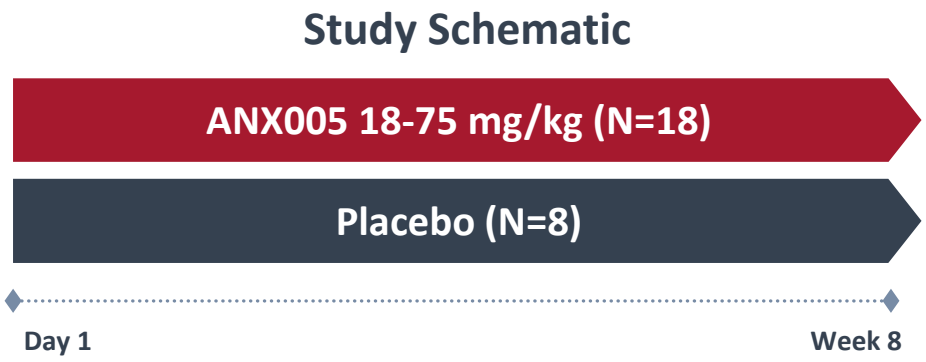
The Dose-Ranging Ph1b Study Laid Foundation for Phase 3 Design

Phase 1b Study Design



- Randomized, double-blind, placebo-controlled study
- N=26[1] Adults with GBS in Bangladesh
- Mean time from onset of weakness: 8.1 days
- Mean GBS-DS at baseline: 4[1]

[1]18-75mg/kg double-blinded dose cohorts

Key Learnings Applied to Phase 3

- ✓ Rapid and full C1q inhibition observed at all doses
- ✓ Stratified by key prognostic factors
  - ✓ MRC
  - ✓ Time from onset of weakness
- ✓ Treat as early as possible (day of randomization)

Phase 3 Designed to Define the Appropriate Duration of Complement Inhibition in GBS

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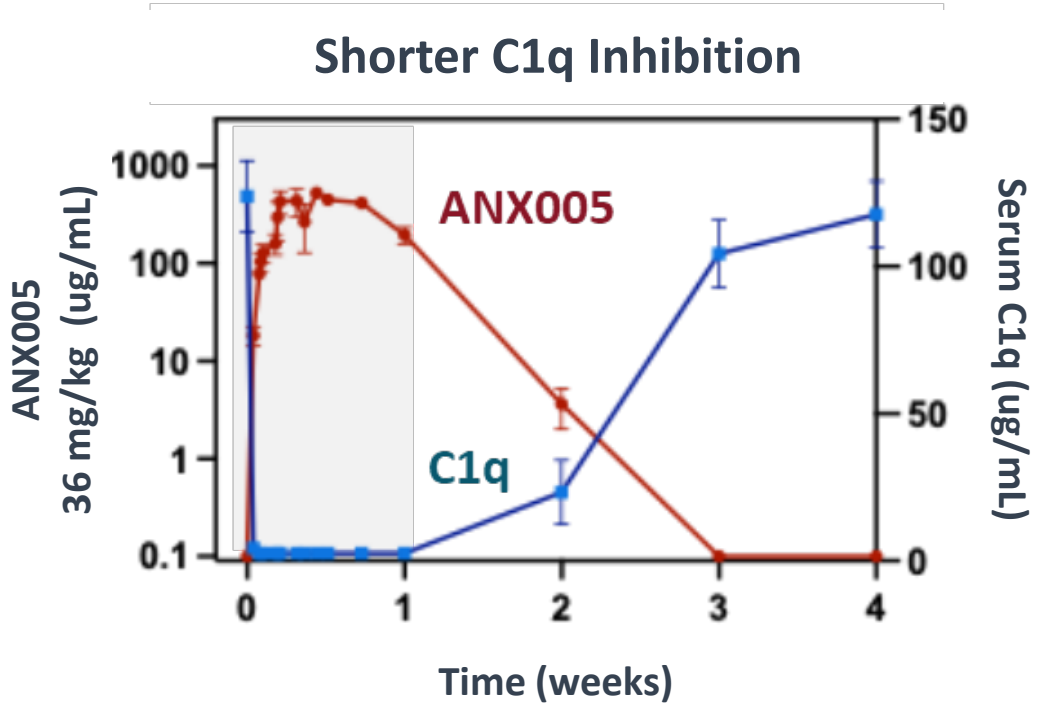
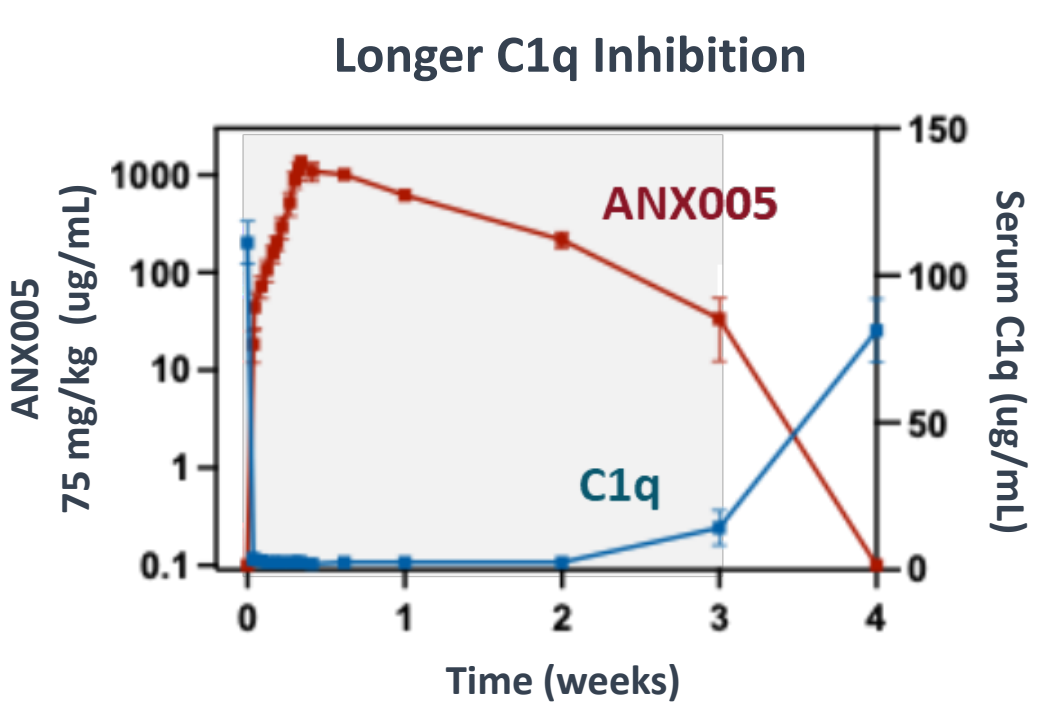
Phase 1b Evaluated Shorter & Longer Durations of Complement Inhibition





- ✓ Immediate full complement inhibition with single infusion
- ✓ C1q inhibition lasts 1-3 weeks with lower and higher dose

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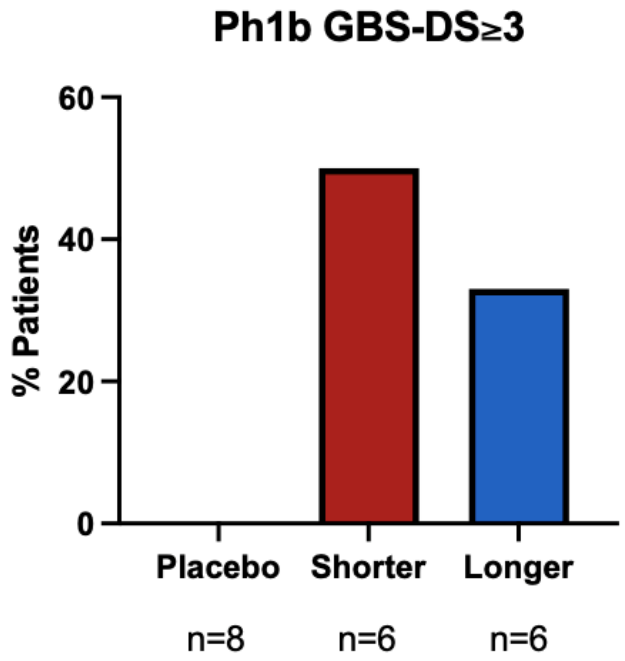
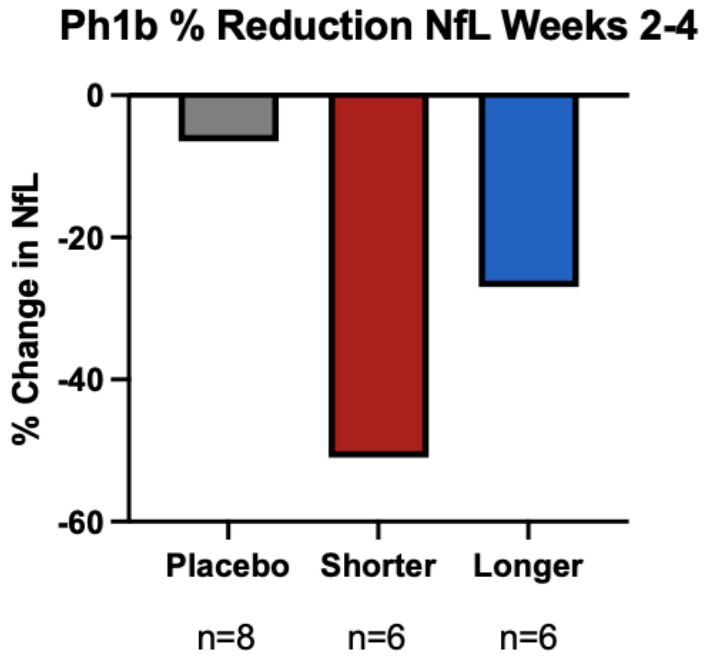
Phase 1b Suggested Shorter Duration of Complement Inhibition had a Greater Effect

Patients Gaining ≥ 3 Points on GBS-DS At Week 8



NfL Reduction Wks 2-4



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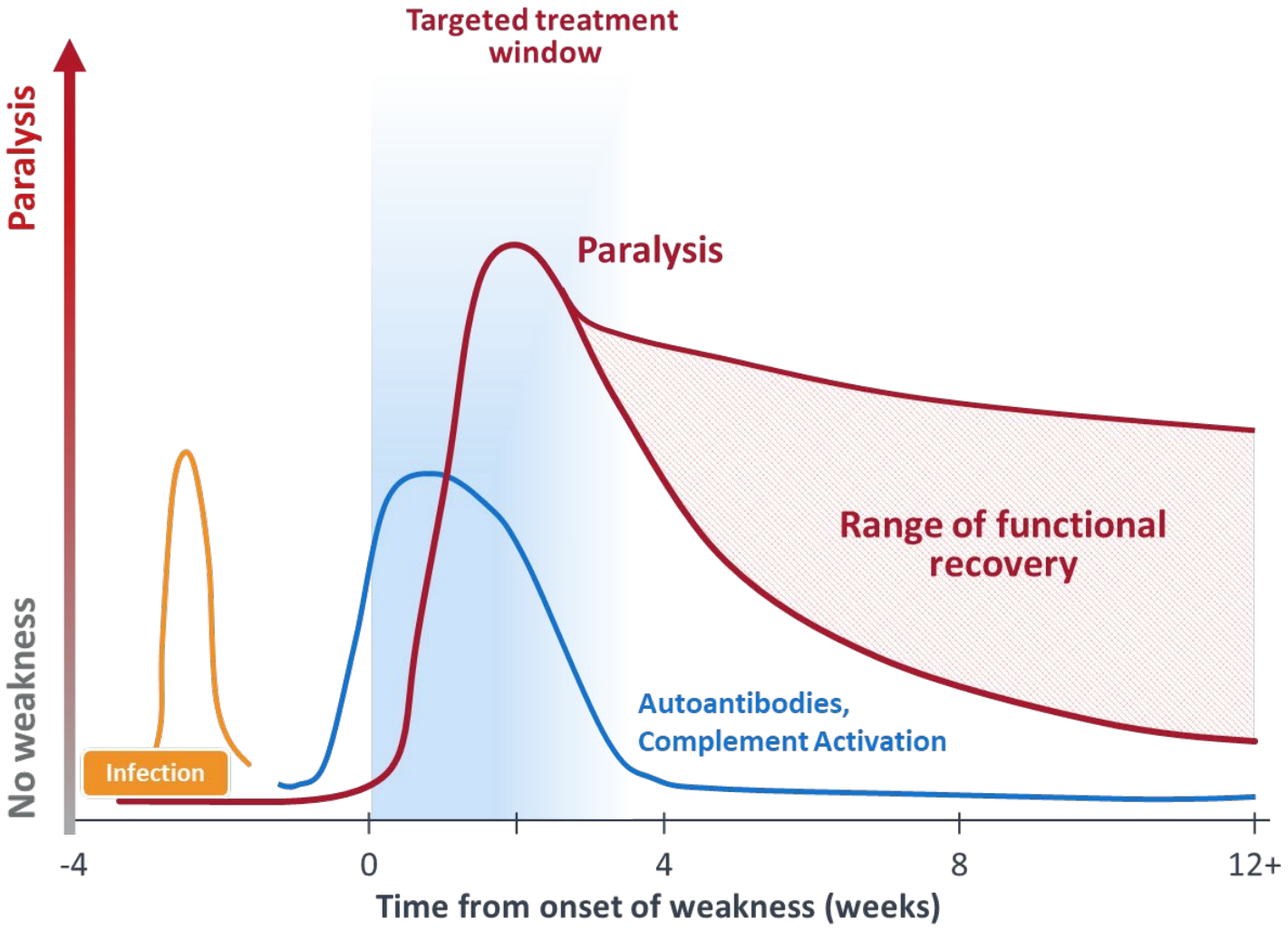
Complement Inhibition During the Active Disease Phase is Key

Acute disease phase of GBS is generally short and varies by patient



- GBS has an acute disease phase followed by spontaneous recovery
- Objectives of anti-C1q treatment in GBS
  - ✓ <u>Block</u> complement-mediated nerve damage during the acute disease
  - × <u>Do not block</u> complement-facilitated nerve repair during recovery phase
- Target treatment window is likely within first 2 weeks

1. van den Berg B et al. *Nat Rev Neurol*. 2014;10(8):469-482. 2. Leonhard SE et al. *Nat Rev Neurol*. 2019;15(11):671-683.

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Pivotal Phase 3 Trial of ANX005 in GBS

Randomized, Double-Blind, Placebo-Controlled Study (Best Supportive Care, no IVIg or PE)

PATIENT SELECTION

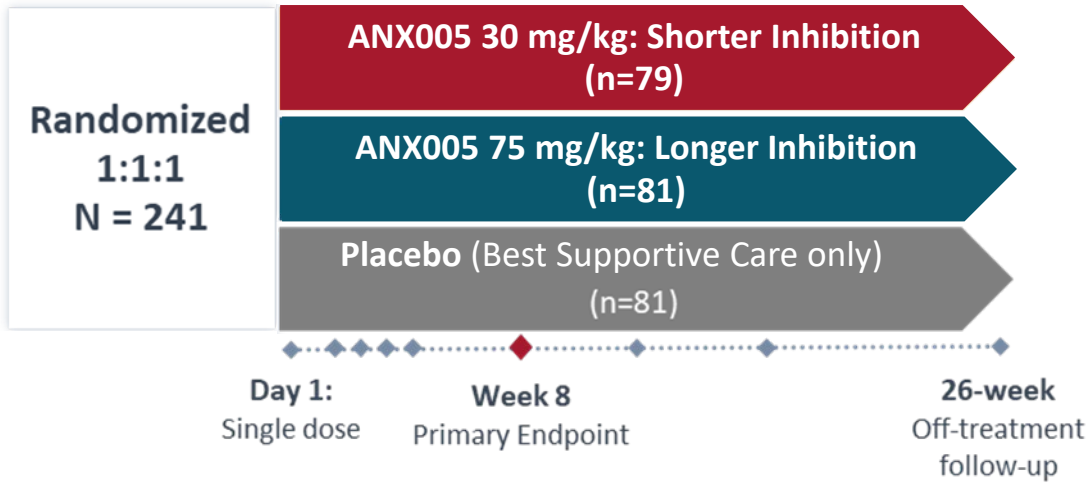
- Baseline GBS-DS score 3-5
- <10 days from onset of weakness
- Stratified by baseline prognostic factors: muscle strength and time from onset of weakness
- Males & females 16 years of age and older

KEY ENDPOINTS

- **Primary Outcome Measure:** GBS-DS[1] at week 8: well-accepted regulatory endpoint assessing functional status
- **Secondary Endpoints:** Muscle strength (MRC sumscore), Motor Disability (ONLS), Duration of Ventilation

[1]Analyzed using a proportional odds model, a common statistical analysis method (van Leeuwen, et al., 2019, doi.org/10.1371/journal.pone.0211404)

2 DOSES SELECTED TO DETERMINE MOST EFFECTIVE DURATION OF INHIBITION



Conducted at Sites in Bangladesh and Philippines

Topline Results Subject to Change

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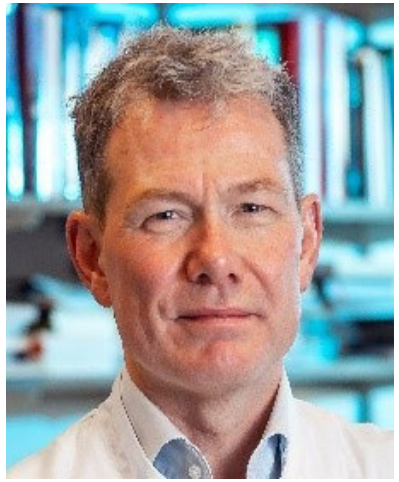
Topline Results of the Phase 3 Trial of ANX005 in patients with Guillain-Barré Syndrome will be presented at the Hughes Clinical Highlights Session

5:00pm, Room 517d

Panel Discussion

David R. Cornblath, MD
Professor Emeritus
John Hopkins University
Medical Center



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