Potential of Efgartigimod in Chronic Inflammatory Demyelinating Polyneuropathy

December 5, 2019 - New York City

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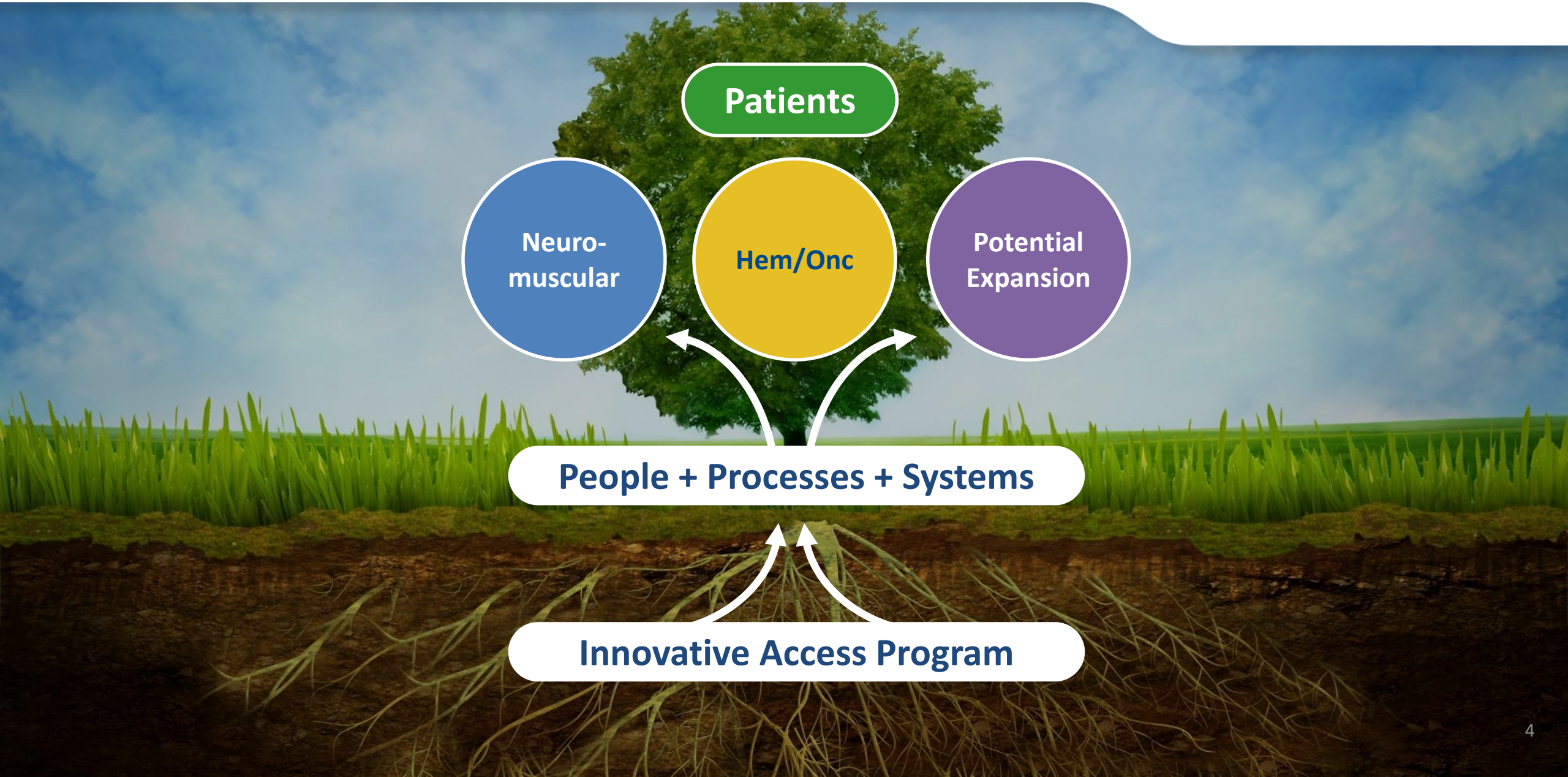
Agenda

4:30 pm – 4:35 pm	**Welcome and Introduction** *Tim Van Hauwermeiren, CEO*
4:35 pm – 5:25 pm	**Chronic Inflammatory Demyelinating Polyneuropathy** Treatment challenges and high medical unmet need *Dr. Richard Lewis, M.D., Cedars-Sinai Medical Center*
5:25 pm – 5:40 pm	**Rationale to Target CIDP with Efgartigimod** *Erik Hofman, Ph.D., Principal Scientist*
5:40 pm – 5:55 pm	**Phase 2 ADHERE Trial Design of Efgartigimod in CIDP** *Wim Parys, M.D. CMO*
5:55 pm – 6:10 pm	**Efgartigimod: Subcutaneous Development** *Keith Woods, COO*
6:10 pm – 6:30 pm	**Q&A**

Guest: Lisa Butler, Executive Dir. GBS/CIDP Foundation International

argenx 2021:
Becoming a Global Integrated Immunology Biotech



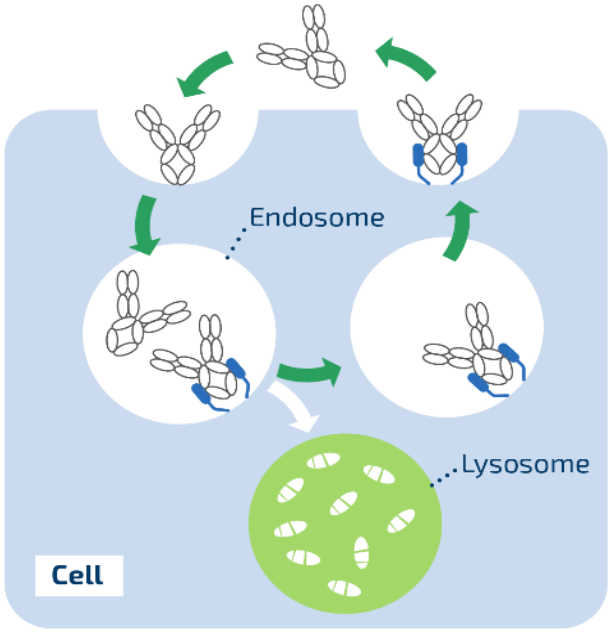
Efgartigimod: Human IgG1 Fc Fragment with Proprietary ABDEG™ Mutations

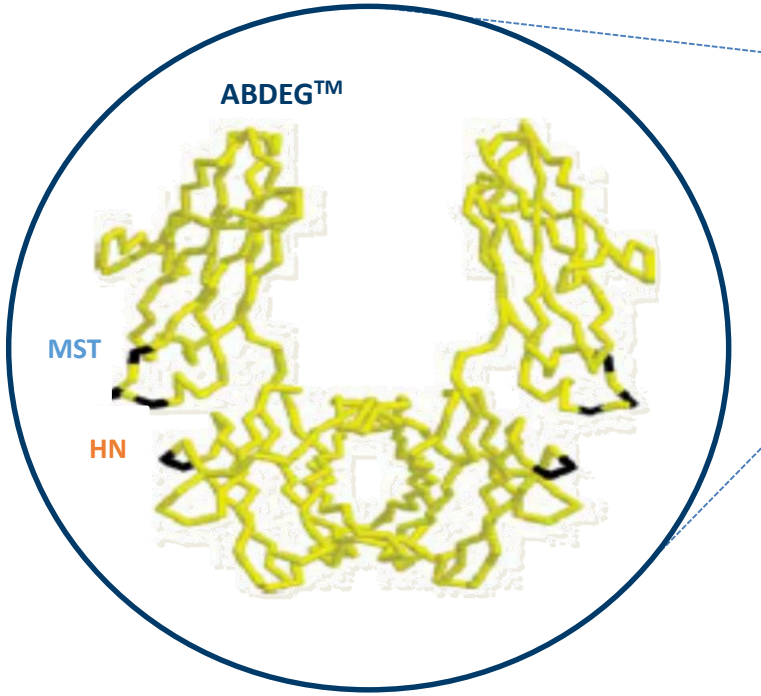
Exploits natural Fc/FcRn interaction and retains pH dependent binding of IgG

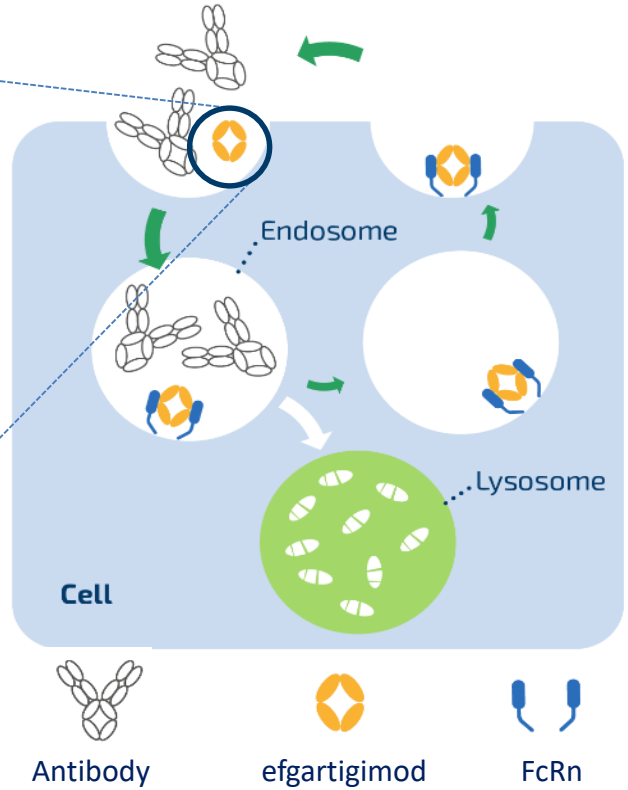
IgG antibodies recycle through FcRn…

efgartigimod potently blocks FcRn…

Leading to IgG elimination







Roopenian et al. 2007, Nat Rev Immunol. Vaccaro et al. 2005, Nat Biotech. Ulrichts et al. 2018, J Clin Invest.

Efgartigimod: Pipeline-in-a-Product Opportunity

Clinical proof-of-concept achieved for neuromuscular and hematology indications

Landscape of IgG-mediated severe autoimmune diseases (sampling)

Immune Thrombocytopenia

Myasthenia Gravis

Multiple Sclerosis

Scleroderma

Rheumatoid Arthritis

Anca Vasculitis

Lupus

Pemphigus

Bullous Pemphigoid

Epidermolysis Bullosa Acquisita

Solid Biology Rationale

Disease proven to be predominantly mediated by pathogenic IgGs

Feasible for Biotech

Orphan potential, economically viable, efficient clinical & regulatory pathway

Proof-of Concept:

Myasthenia Gravis ✓	Immune Thrombocytopenia ✓	Pemphigus Vulgaris
Neuromuscular Diseases	Hematology Disorders	Blistering Diseases

Therapeutic Area Beachheads with Expansion Possibilities into Adjacent Indications

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Efgartigimod Portfolio: Multiple Formulations in Development

Optionality for patients, physicians and payors across indications and geographies

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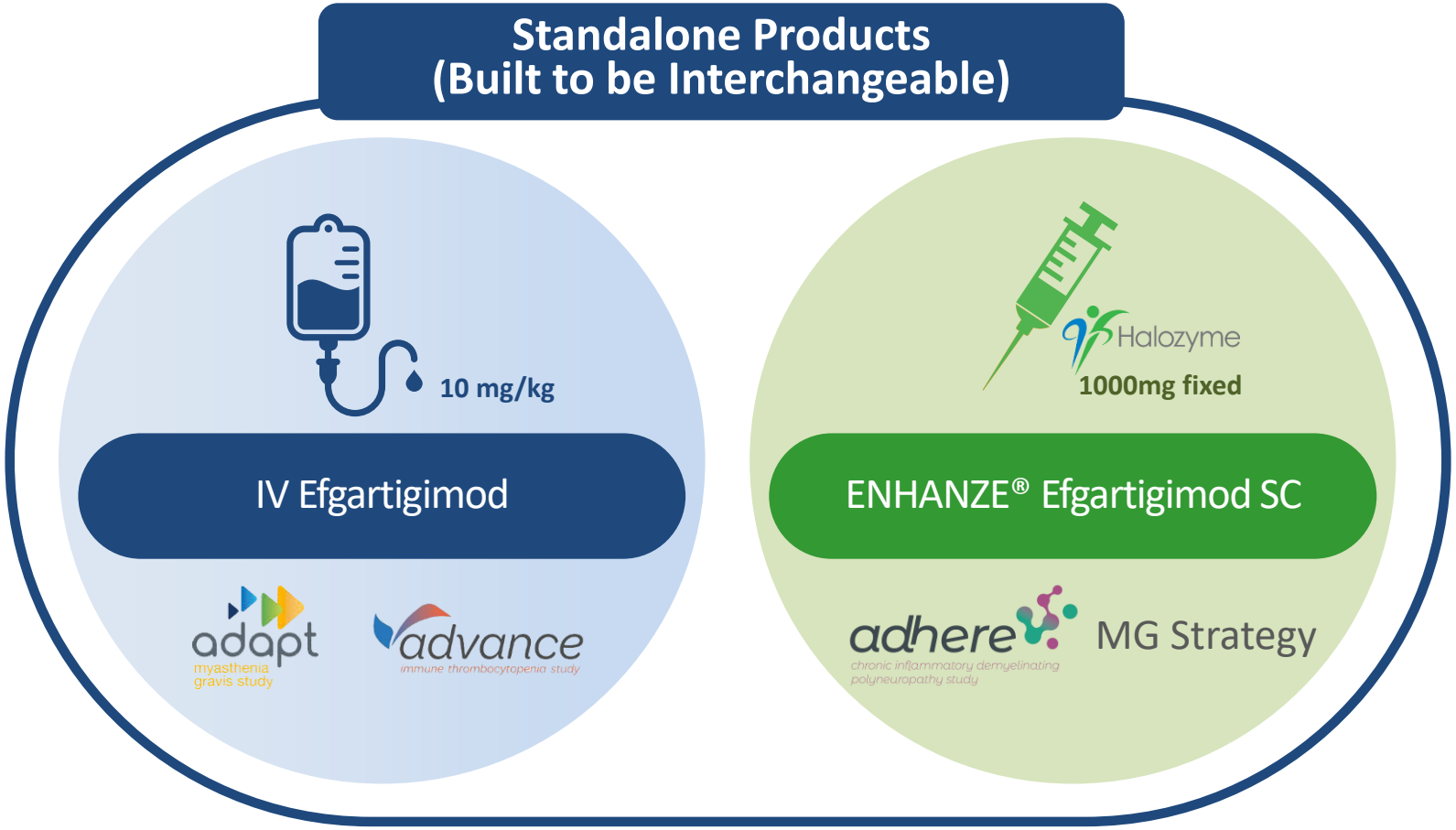
Standalone Products (Built to be Interchangeable)



60-minute infusion

Subcutaneous injection

IV infusion induction
SC injection maintenance

Three Formulations Available for Use in Future Studies

What We Will Show You Today

CIDP pathophysiology involves cellular and humoral immunity

Clinical evidence may be ahead of scientific understanding

- Removing IgGs with increased specificity shows consistent efficacy
- Translational biology ongoing to characterize autoantibodies and autoantigens
- Identified IgG autoantibodies shown to be pathogenic

ADHERE trial to incorporate ENHANZE® efgartigimod SC formulation

- Multiple risk-mitigating filters including GO-NO GO decision

ENHANZE efgartigimod SC formulation has demonstrated comparable IgG lowering to IV infusion

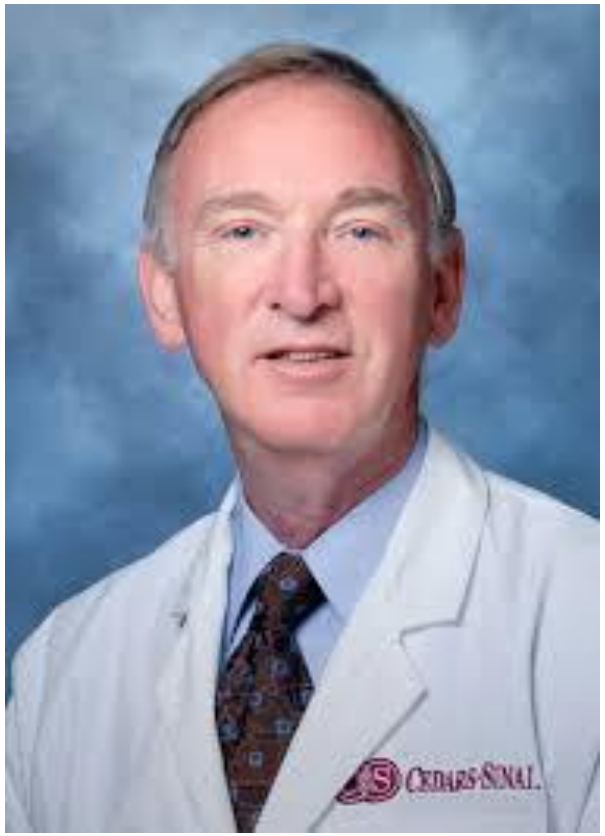
Market opportunity and unmet need for CIDP are significant

Chronic Inflammatory Demyelinating Polyneuropathy

Treatment challenges and high medical unmet need

Richard Lewis, M.D., Cedars-Sinai Medical Center

Professor Richard A. Lewis, M.D.



Cedars-Sinai Medical Center
Professor, Neurology
Director, Electromyography Laboratory

Research interests: CIDP, Guillain-Barre Syndrome, ALS, inherited neuropathies (CMT), Myasthenia Gravis

Dr. Lewis joined Cedars-Sinai in 2012. He previously served as vice chief of neurology and director of clinical neurophysiology at Harper University Hospital in Detroit. He was professor and associate chair of neurology at Wayne State University School of Medicine from. 1993-2012. He has held academic positions at University of Pennsylvania, University of Connecticut and was in a group practice in Norfolk, Virginia.

Dr. Lewis has been Chair of the Inflammatory Neuropathy Consortium and is currently President-Elect of the Peripheral Nerve Society. He may be best known for the discovery and exploration of an autoimmune disorder that bears his name: Lewis-Sumner syndrome, a variant of CIDP. He is on the MAB of the GBS-CIDP Foundation International and has published extensively on the inflammatory neuropathies.

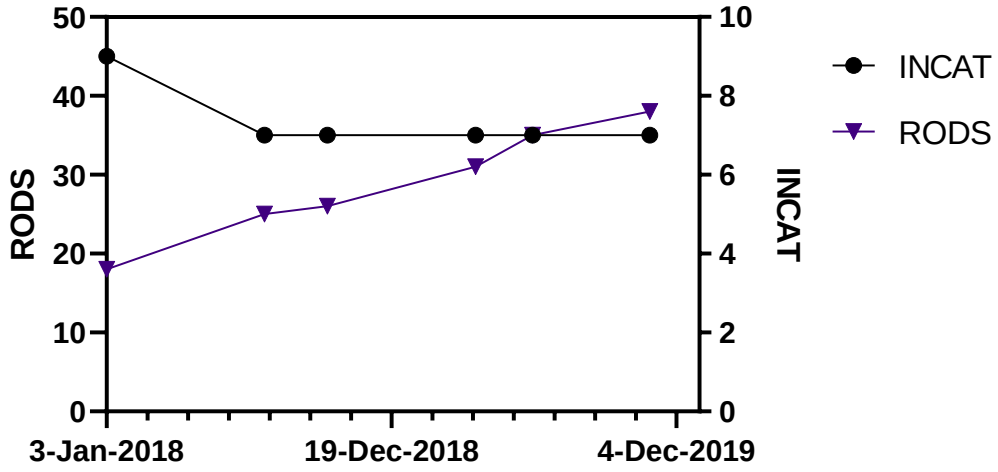
Disclosures

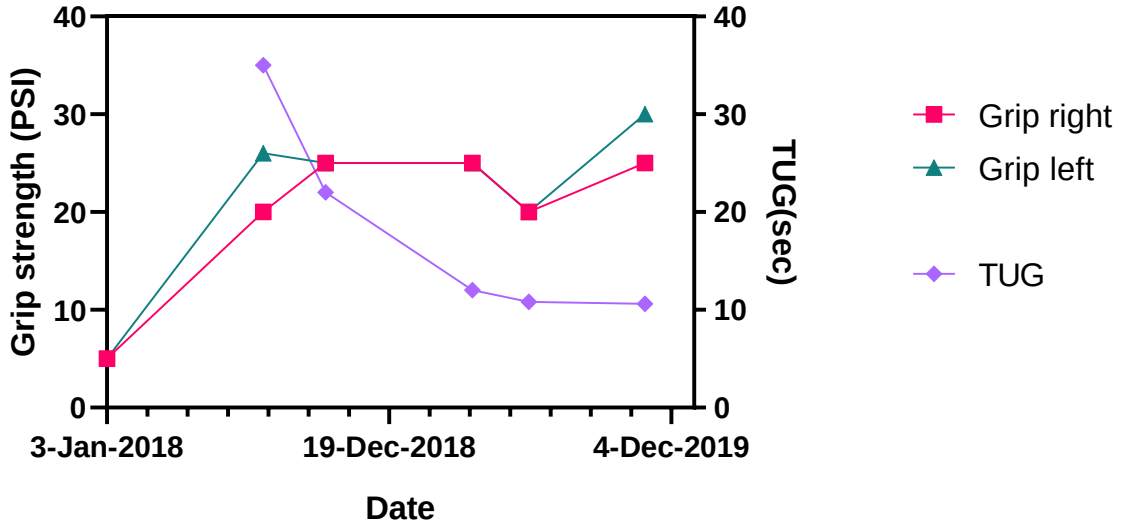
- Consultant for CSL Behring, Pharnext, Argenx, Momenta, Biotest, Sanofi, Alexion, Annexon, Pfizer, Takeda
- Advisory committee for argenx ADHERE trial; Chair of CIDP confirmation committee
- Steering committee member for CSL Behring PATH trial on Hizentra
- Honorariums and Ad Boards from Akcea, Alnylam
- Medical Advisory Boards: GBS-CIDP Foundation International; MG Foundation of America; MG Foundation of California; Foundation for Peripheral Neuropathy
- President-elect of Peripheral Nerve Society (Executive Board member)

Case 1: Residual Deficits from Aggressive Disease

- **April 2018**: 51 yo woman with numbness and tingling of hands and feet
- **June 2018**: Normal strength; increasing numbness and incoordination
  - EMG prolonged distal motor latencies, slow velocities and F latencies with normal needle EMG
  - CSF protein 208 (normal < 45 mg/dl); multiple oligoclonal bands
- **July 2018**: IVIG for CIDP – high doses for 3 months; flu-like symptoms and no improvement
- Started on oral prednisone
- **October 23, 2018** (my first assessment): severe weakness of ankles, moderate weakness all muscles in arms and legs; unable to stand and all reflexes lost
- **November 2018:** 1000mg pulse Medrol started in given weekly for 4 weeks- no worse but no better.
- PLEx given 12/13-12/26 for 6 sessions; noticed some improvement
- **January 2019:** started to see demonstrable improvement.
  - Could use hands, brush hair, walk with assist 150 feet

Outcome Measures Document Clinical Status





- Prednisone tapered to current dose of 25 mg QOD
- Persistent severe weakness at ankles; will likely need braces forever.
- Intrinsic hand muscles atrophied and weak; tremor.
- Normal grip strength for her would be > 60 psi; unchanging grip strength shows axonal loss to hands and forearms - probably at maximum recovery. Improving RODS shows disability can be overcome despite persistent weakness but 38/48 shows moderate functional problems.

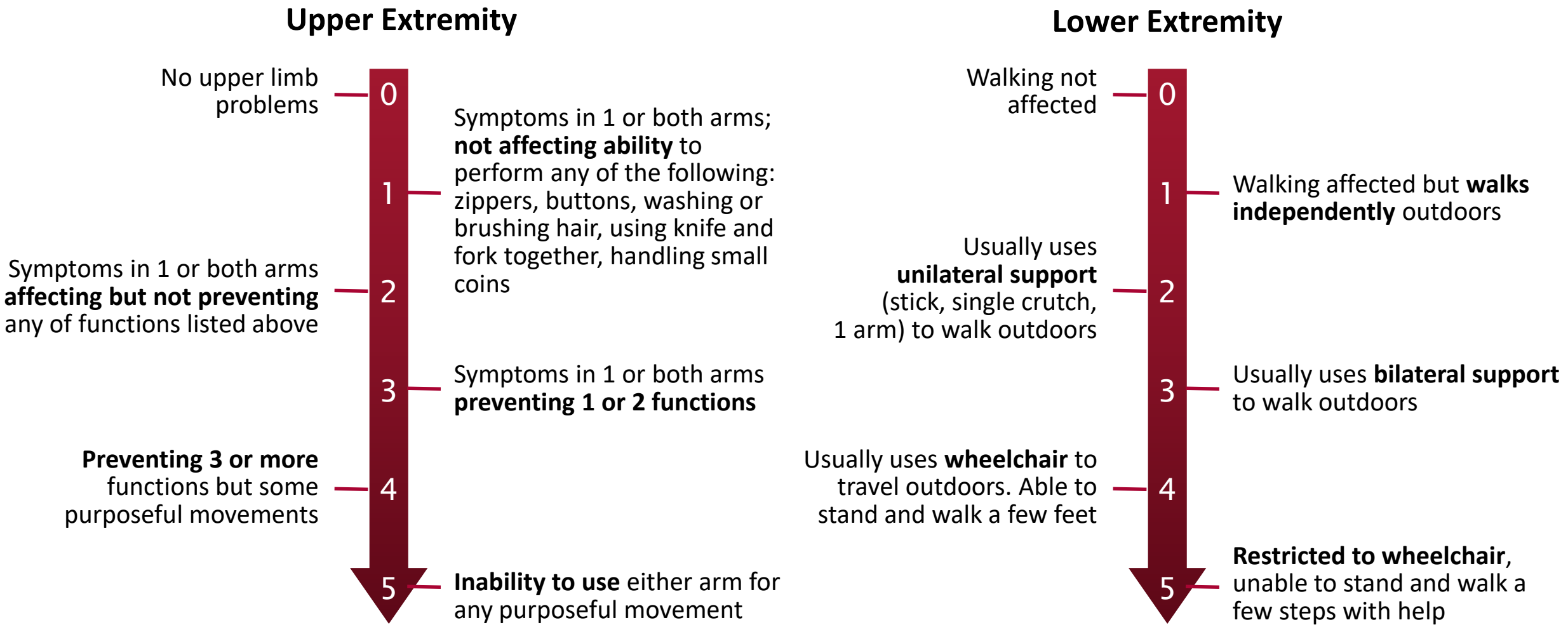
Lessons From Case 1

- CIDP can progress over a few months to severe disability (wheelchair)
- Current treatments not always effective (IVIg failure) and delay in control can lead to persistent disability
- PLEx effective in rapidly stabilizing disease; high-dose steroids controlled disease
- Grip, RODS and TUG reflect disease activity

Assessment tools for clinical trials and practice

INCAT (Inflammatory Neuropathy Cause and Treatment) DISABILITY SCALE

Primary outcome measure in CIDP trials



I-RODS: Inflammatory (Neuropathy) Rasch-built Overall Disability Scale

(van Nes SI…..Merkies IS. Neurology 2011; 76:337)

Not possible [0] **With some difficulty [1]** **Without any difficulty [2]**

1. read a newspaper/book?
2. eat?
3. brush your teeth?
4. wash upper body?
5. sit on a toilet?
6. make a sandwich?
7. dress upper body?
8. wash lower body?
9. move a chair?
10. turn a key in a lock?
11. go to the doctor?
12. take a shower?
13. do the dishes?
14. do the shopping?
15. catch an object (ball)?
16. bend and pick up an object?
17. walk one flight of stairs?
18. travel by public transportation?
19. walk and avoid obstacles?
20. walk outdoor < 1 km?
21. carry and put down a heavy object?
22. dance?
23. stand for hours?
24. run?

GRIP STRENGTH: QUICK and RELIABLE

Martin Vigorimeter

Jamar

Timed Up and Go: TUG

- Used in joint replacements and to assess risk of falls in elderly
  - Patient sits in chair
  - Walks 3 meters
  - Turns around
  - Sits back in chair

- Easy to administer and can be done at home

- Relevance for CIDP
  - Getting up and down from chair may be particularly important in CIDP

MRC sum score

Muscle pairs:

- arm abductors,
- elbow flexors,
- wrist extensors,
- hip flexors,
- knee extensors
- foot dorsal flexors

- Score each muscle group
  - *0 = no movement, no contraction*
  - *1 = visible contraction without movement*
  - *2 = movement, but only with gravity eliminated*
  - *3 = movement against gravity*
  - *4 = movement against resistance, but weaker than normal*
  - *5 = normal strength*
- Range: 0 (total paralysis) to 60 (normal strength)

Patient 2- Teen unable to tolerate IVIg and Corticosteroids

- 18 yo woman developed bilateral proximal and distal weakness with sensory symptoms.
  - Areflexic; nerve conduction studies revealed velocities ~ 20 m/sec; marked temporal dispersion
- Hospitalized; treated with IVIg for GBS; progressed for >8 weeks - unable to walk
  - Did not respond to induction IVIg; had remarkable improvement after 2nd treatment with 1g/kg
  - Severe headaches with each IVIg consistent with migraines; in bed for 4-5 days
- Trial of pulse steroids caused severe and unacceptable agitation and depression
- Retrial of IVIg with different brand caused same headaches.
- Switched to SCIg; receives 20gm/wk in one 2 hour infusion/wk
  - Equivalent to 1 gm/kg IVIg every 3 weeks (60 Kg)
- Has been on SCIg for >3 years. No symptoms and normal examination except for reduced reflexes. Fully active - has been able to travel to 3 continents taking her SCIg with her. Has had some injections site inflammation but otherwise no side effects.

Side effects of medications can be severe; treatments require continued use but can be very effective

Advantages of SC Treatments over IV Infusions

- **SC patients control treatment; can take when convenient**
- **IV access not an issue**
- **Easier to travel; less bound to IV schedule**
- **No need to go to infusion center or have home infusion invasion**
- **Side effect profile different and significantly less than IV (in case of Ig)**
- **Less risk of bolus**

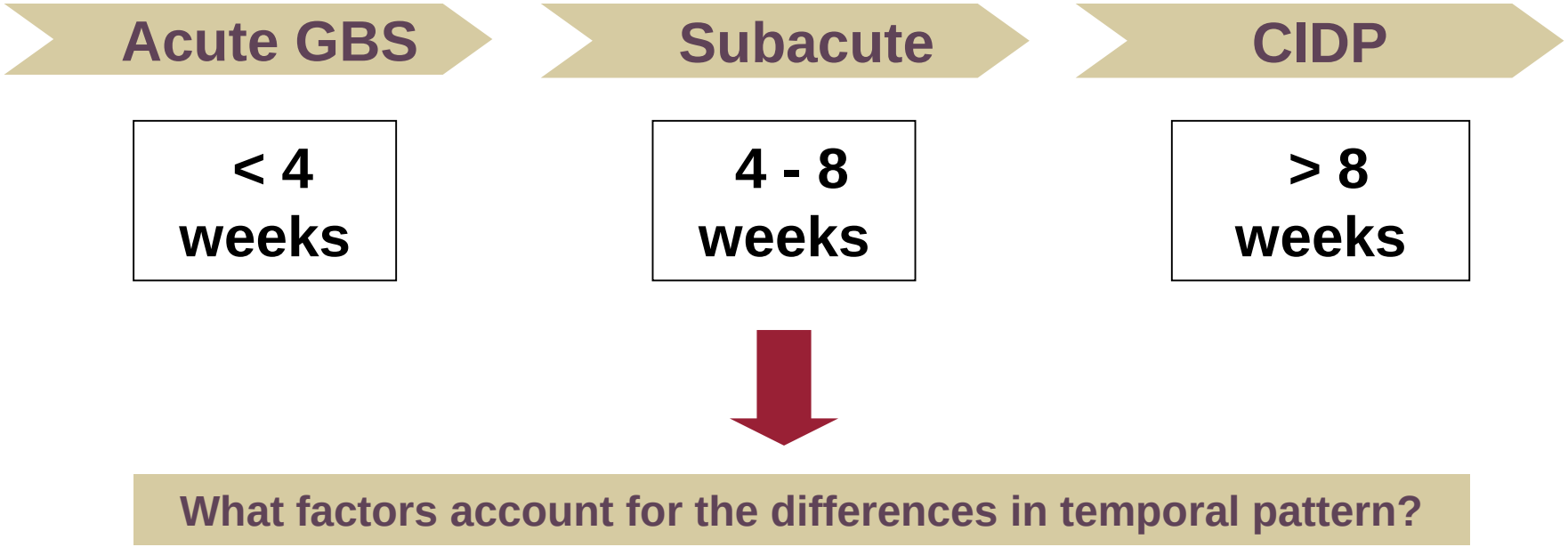
Case 3: College Student Had to Miss Semester Due to CIDP

- 20 yo man develops progressive weakness of arms and legs over 3 months
- “Classic CIDP” with proximal and distal weakness, areflexia, elevated CSF protein and nerve conduction slowing of 20-28 m/sec with conduction block and temporal dispersion.
- IVIg and corticosteroids ineffective; required wheelchair; missed semester of college; unable to live in dorms or navigate campus
- Cyclophosphamide 6 monthly pulse IV treatment controlled disease; remained in remission for > 4 years with no treatment; residual mild ankle weakness; completed college
- However, during treatments, blood counts dropped, had dangerous infection from which he fortunately recovered
- Still has future risk of malignancy due to the treatment; possible fertility issue

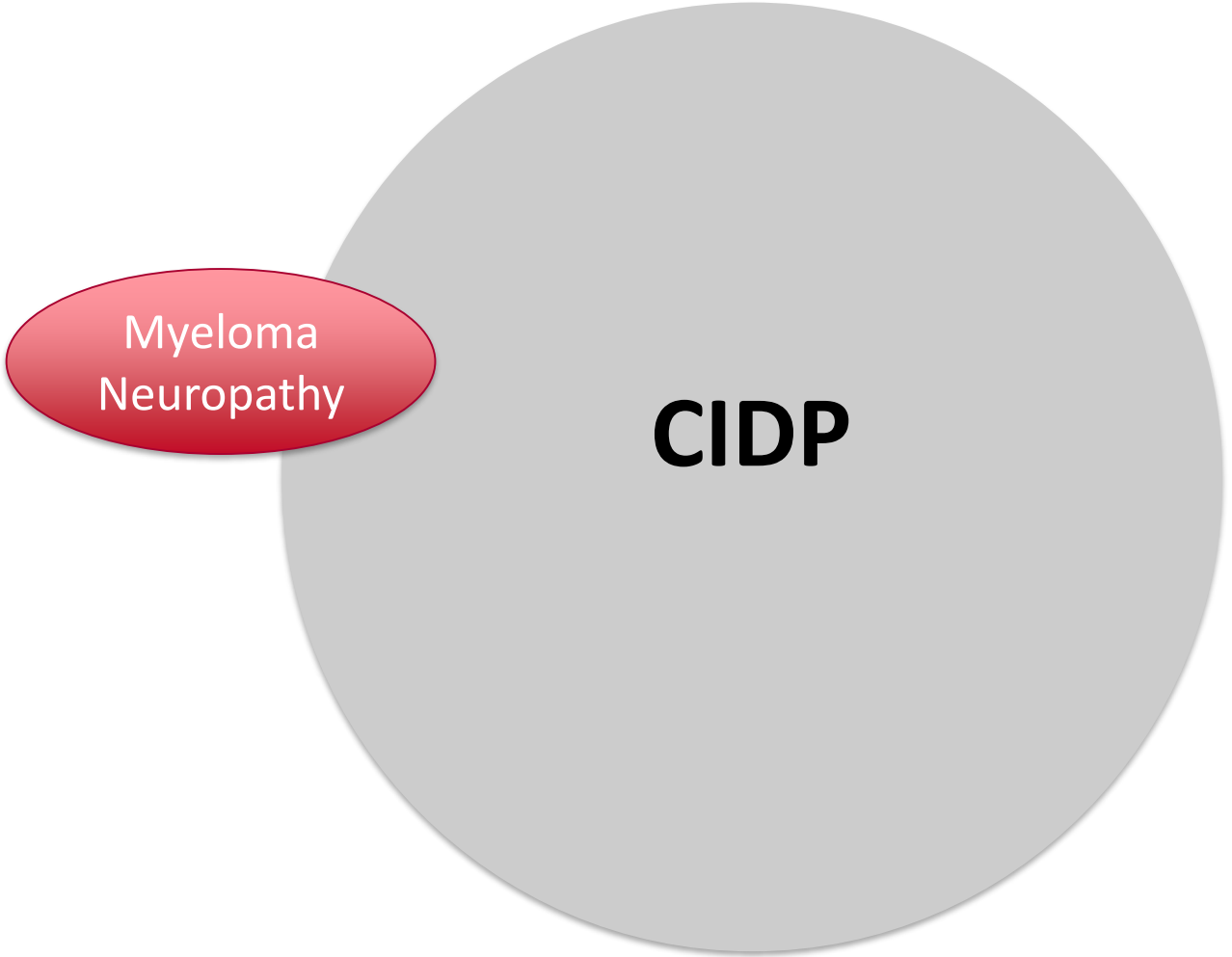
Immunosuppression can be very effective but short and long term risks

What is CIDP? Chronic Inflammatory Demyelinating Poly(Radiculo)Neuropathy

- First described in **1975** by Peter Dyck and colleagues at Mayo Clinic- 53 patients with sensorimotor neuropathy, elevated CSF protein and nerve conduction slowing.
- Many responded to corticosteroids
- Thought to be related to Guillain Barre Syndrome

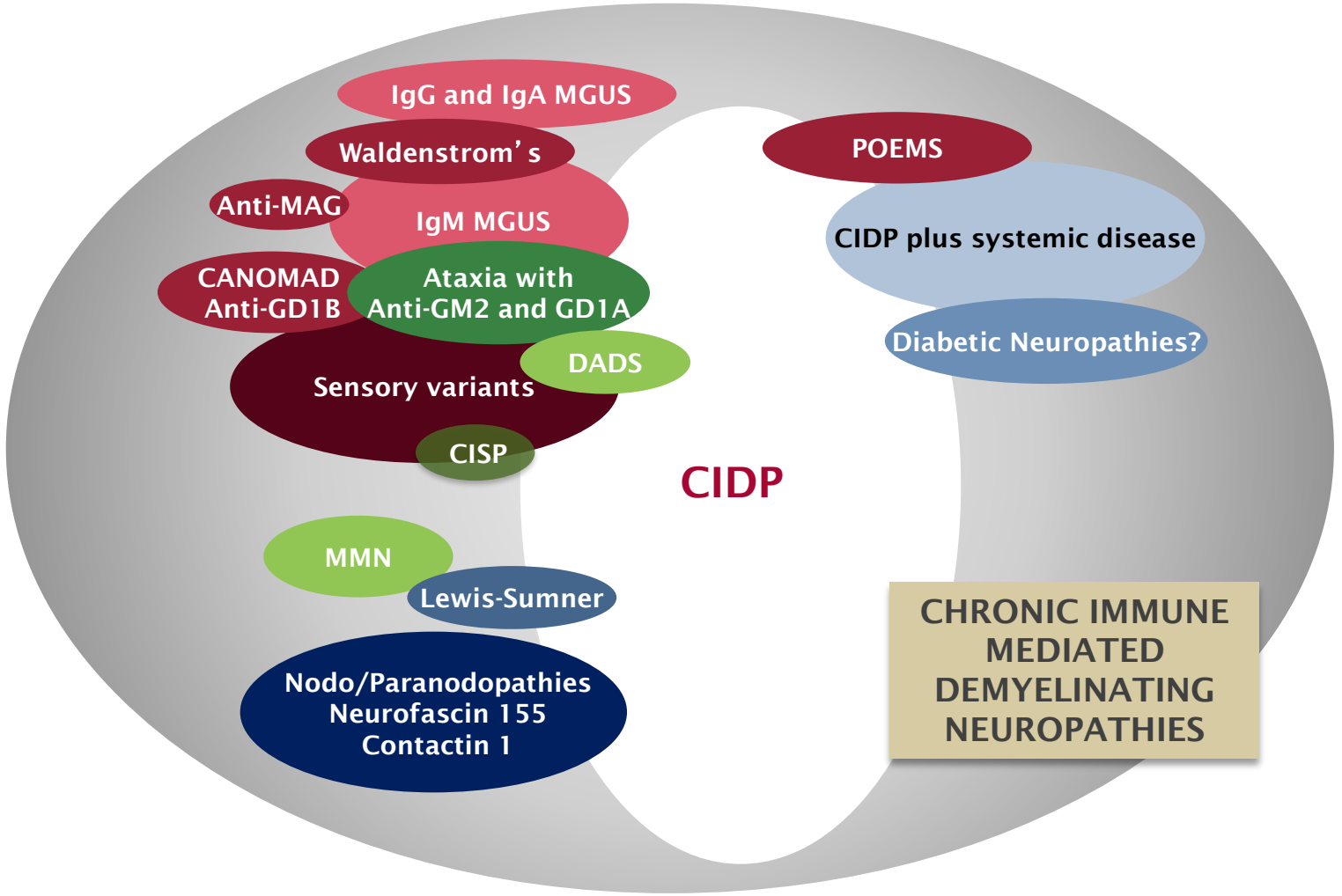


1980- CIDP Is A Disease



2019: A Bit More Complicated

- Classification recognizes not all immune disorders are CIDP
- Some IgM paraprotein neuropathies behave like CIDP but most do not.
- MMN is not CIDP but L-SS is.



Demographics of CIDP

- Incidence of 1/100,000 per year
- Prevalence of 2-10/ 100,000 depending on criteria used
  - 4.7/100K with EFNS/PNS but 2.0/100K with AAN
  - 80% of AAN-/EFNS+ responded to therapy
- **50% severely disabled at some stage of illness; 15% with persistent severe disability**
- Prognosis*:
  - 11% in long term remission for 5 years
  - 20% off-drug for 2-3 years
  - **70% need ongoing treatment (progressive)**

* Gorson KC et al. CIDP Disease Activity Status (CDAS) 2010

The EFNS/PNS Guidelines (2010): The Best So Far Clinical Criteria

TYPICAL

- > 2 months
  - Relapsing or progressive
- Symmetric Prox/distal
- Reduced DTRs

ATYPICAL

- DADS
- Pure sensory
- Multifocal (Lewis-Sumner)
- Nodo/Paranodopathies
- Pure motor
- Focal (eg. Plexus)

(JPNS 10:220-228 2005; Revised E Journal of Neurology 2010, 17: 356–363)

Clinical Criteria - The Best So Far: The EFNS/PNS Guidelines

(JPNS 10:220-228 2005; Revised E Journal of Neurology 2010, 17: 356–363)

- Evidence/consensus based; Clinical, electrodiagnostic and supportive aspects
  - Definite, probably, possible

- **Clinical diagnostic criteria**
  - **Typical:** > 2 months, relapsing or progressive, symmetric proximal/distal, reduced DTRs
  - **Atypical:** DADS, Lewis-Sumner, pure sensory, pure motor, focal (eg. Plexus), CNS involvement

- **Electrodiagnostic criteria** (DML, Conduction Velocity, F wave prolongation, Conduction Block Distal CMAP duration)

- **Supportive criteria** (CSF protein, MRI, nerve biopsy, objective clinical improvement with immune treatment)

Classic Features of Typical CIDP

- Symmetric
- Progressive or relapsing > 8 weeks
- Areflexia (reduced reflexes)
- **Distal and proximal** weakness usually with some sensory component
- Elevated CSF protein
- Multifocal conduction slowing on NCS
- Objective response to immune modulation

I Am Most Proud of This Citation

- Koski CL, Baumgarten M, Magder LS, Barohn RJ, Goldstein J, Graves M, Gorson K, Hahn AF, Hughes RA, Katz J, Lewis RA, Parry GJ, van Doorn P, Cornblath DR. **Derivation and validation of diagnostic criteria for chronic inflammatory demyelinating polyneuropathy.** J Neurol Sci. 2009 Feb 15;277(1-2):1-8.

- **Abstract:** "To develop diagnostic criteria for chronic inflammatory demyelinating polyneuropathy (CIDP), a retrospective series of patients' records diagnosed by ***sexpert*** consensus as CIDP or other chronic polyneuropathies were analyzed……

Clinically "Typical" Disease is Easily Diagnosed

Italian Review of Atypical CIDP (Doneddu PE et al. JNNP 2019)

- 460 patients with CIDP had 19% atypical cases
  - DADS 7%; Pure Sensory 3.5%; LSS 4%; pure motor 4%
  - DADS and LSS- less responsive to IVIg
  - At onset of symptoms 39% atypical
    - 13% DADS and 11% sensory (2 with CISP)
  - 53% progressed to typical; mean duration 5.5 years (1-38)
  - Pure sensory converted in 48% but only 24% of DADS

There may be regional differences: Japan has 40% atypical cases

Italian Review of Atypical CIDP (Doneddu PE et al. JNNP 2019)

DADS (N=34)

- 70% fulfilled EFNS critera-21 definite; 3 probable
- IRODS 39/48 INCAT 1.5
- **Treatment response 64%;**
- **Steroids 56%; IVIg 50%**

Sensory (N=16)

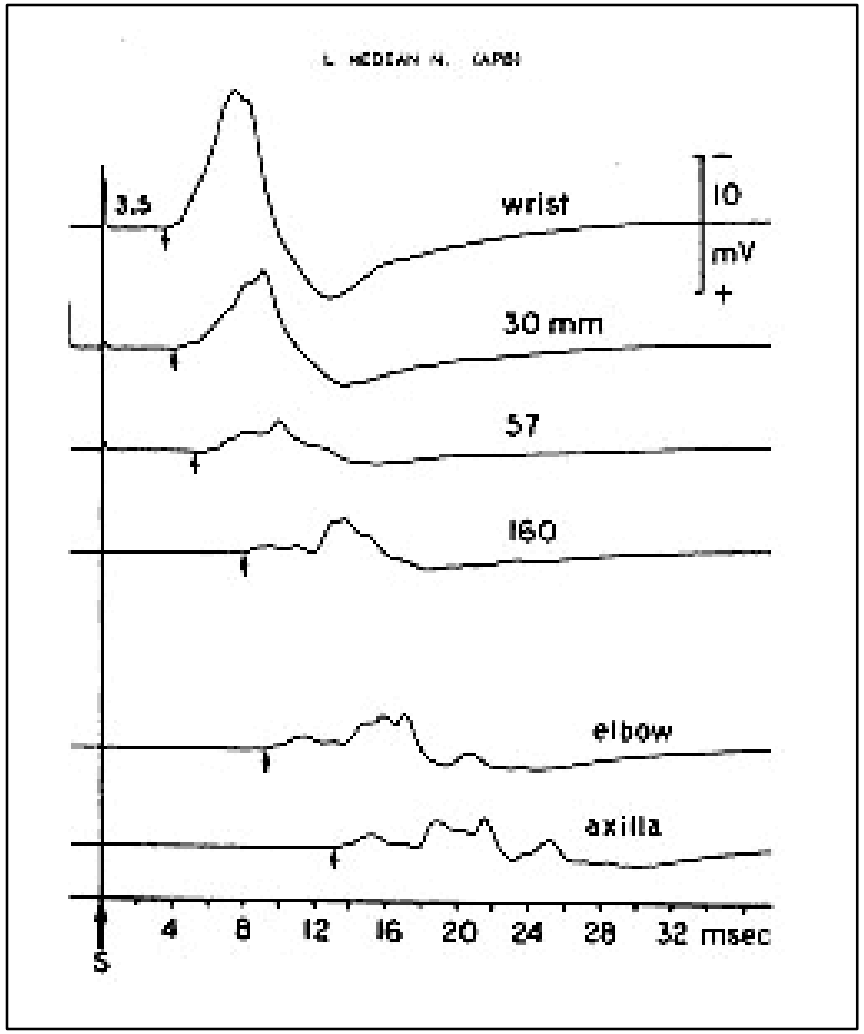
- 75% EFNS
- IRODS 38; INCAT 1.7
- **Treatment response 90%;**
- **Steroids 67% IVIg 86%**

Typical (n=376)

- 82% EFNS
- IRODS 33; INCAT 2.7
- **Treatment response 87%;**
- **Steroids 51%; IVIg 78%**

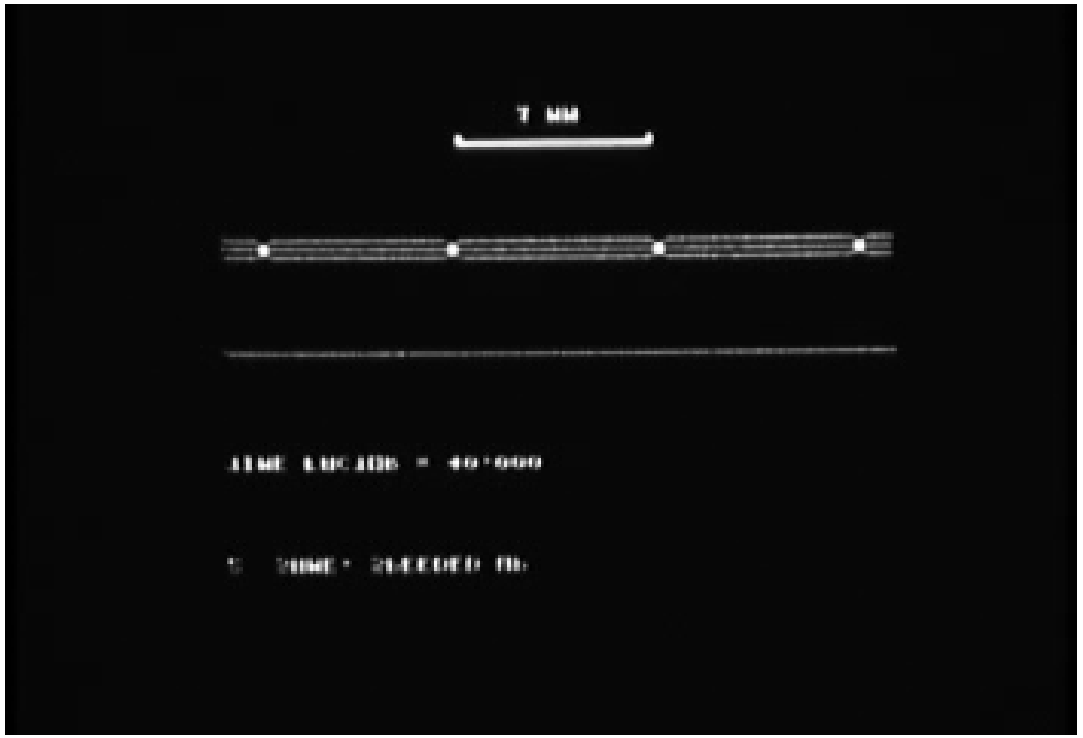
Electrodiagnostic Findings That Suggest Demyelination

- Conduction Block
- Conduction Slowing
- Segmental Slowing
- Temporal Dispersion
- Distal Accentuated Slowing
- Distal Duration Prolongation



Effects of Paranodal Demyelination on Single Nerve Fibers: Conduction Block

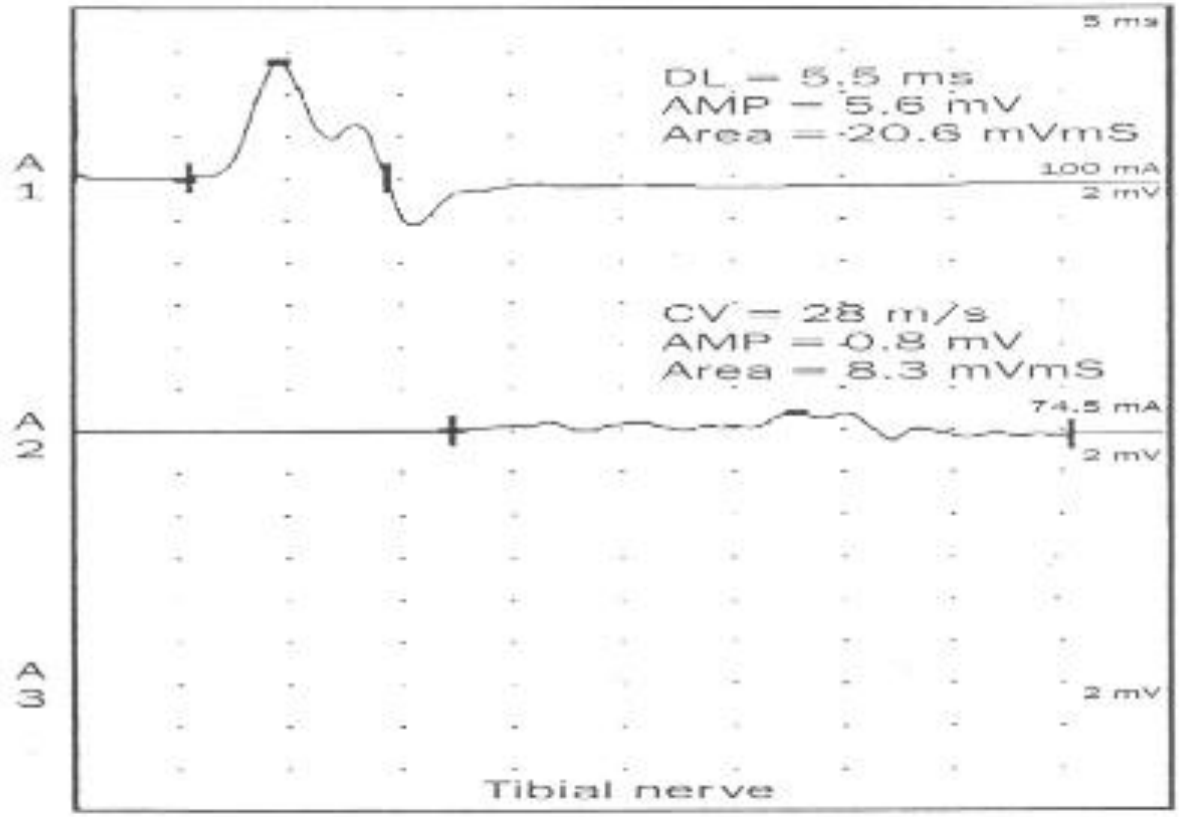
The interruption of action potential propagation due to changes of the Node of Ranvier, paranode or internode without destruction of the axon



EMG Criteria for Demyelination (From Bromberg MB M&N 2011)

- **Distal latency >125% of ULN**
  - Median > 5.5 msec; Ulnar > 4.5 msec
  - Peroneal and Tibial > 6.5 msec

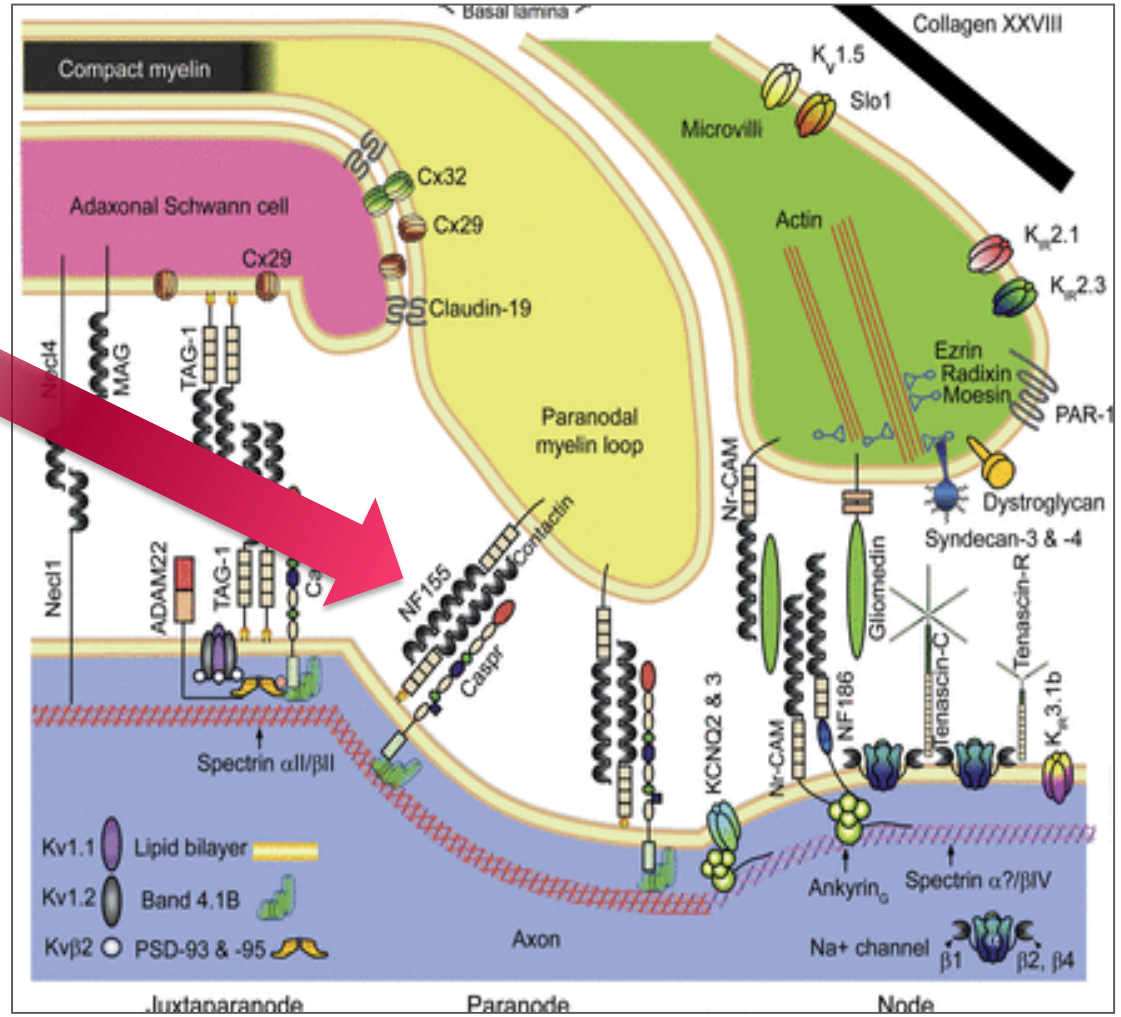
- **Conduction velocity <70% of LLN**
  - **Median and Ulnar < 35 m/sec**
  - **Peroneal and Tibial < 28 m/sec**



Neurofascin-155: Paranodal myelin protein Contactin and Caspr: Axolemmal proteins

- Neurofascin-155 interacts with Contactin-1 and Caspr to form bands that seal the paranodal myelin to the axon restricting the node and hiding the juxta-paranodal K+ channels

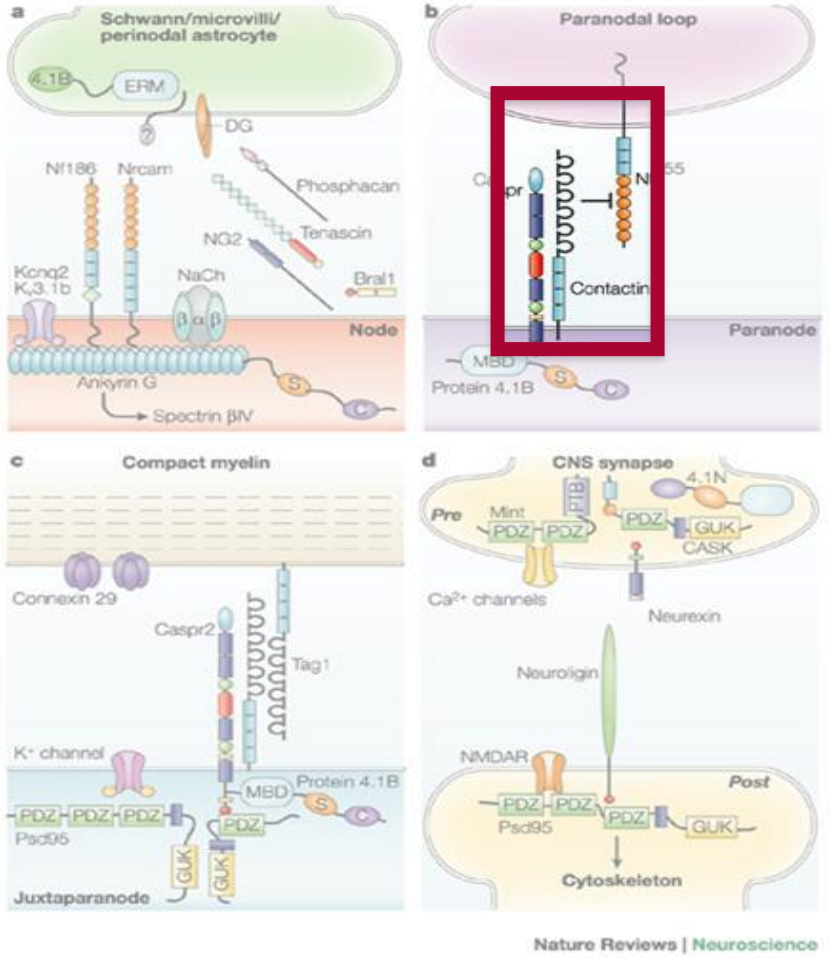
- Knockout mice deficient in these paranodal proteins all have slow NCVs



CIDP with Neurofascin-155 or Contactin-1 Antibodies

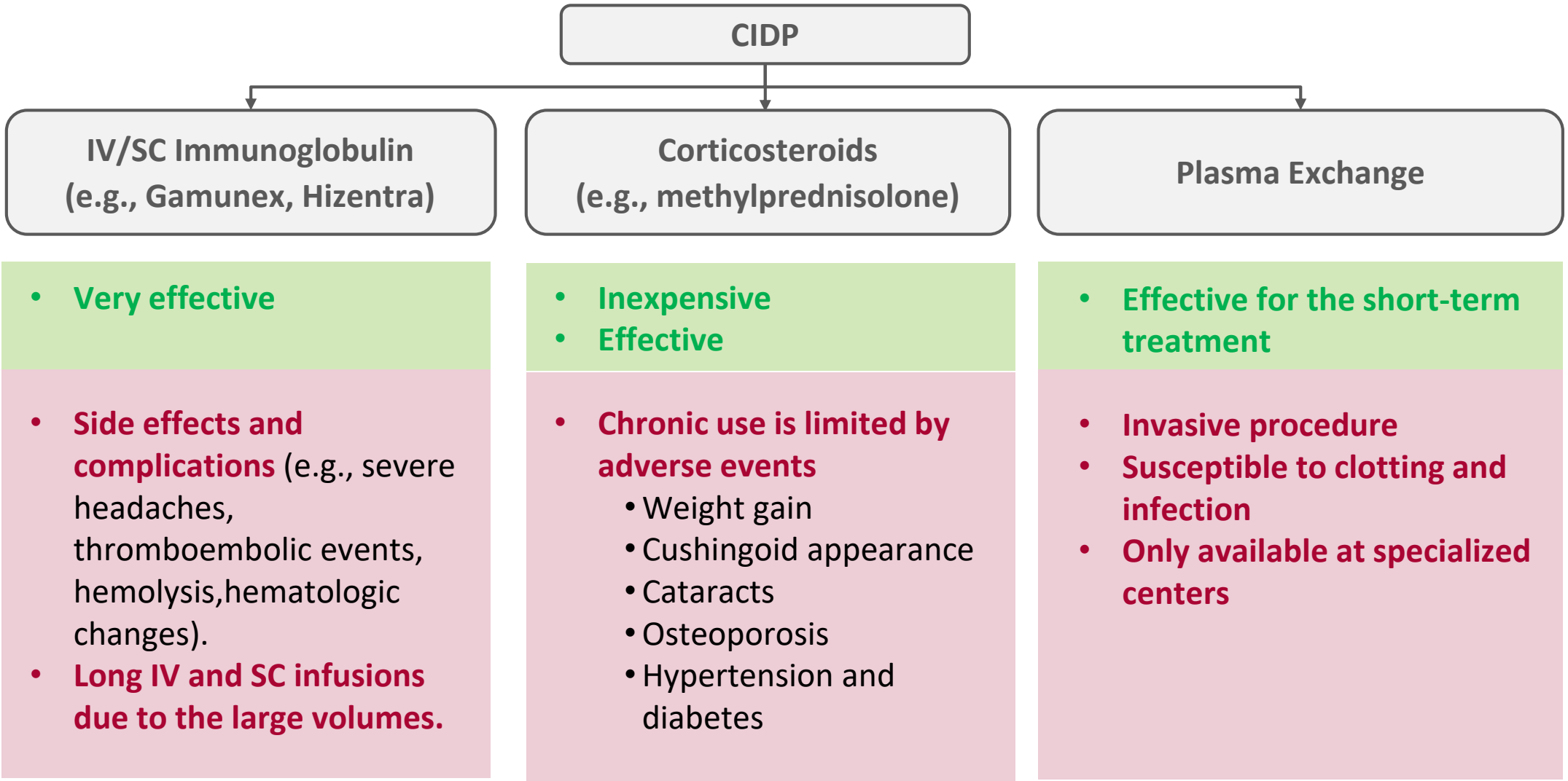
Querol L.… Illa. I. Ann Neurol 2013; Neurology 2014; 2015

- Contactin Ab causes severe CIDP
  - Contactin/Caspr complex Ab in one patient
- Neurofascin Ab severe CIDP with tremor
- Poor response to IVIg
- IgG4 antibodies- not complement mediated
- Rituximab responsive



Treatment of CIDP: Current State of Affairs

First Line Treatments



Immunosuppressive Therapies and Risks: All Carry Risk of Infection, Malignancy

Response in < 3 months

- Cyclosporine
  - Renal, Thyroid, Blood Pressure
- Cyclophosphamide
  - Bone Marrow; Malignancy, infertility
- Methotrexate
  - Stomatitis, Liver

Response in > 4 months

- Azathioprine
  - Blood Counts, Liver
- Mycophenolate
  - Blood Counts

POSSIBLE TREATMENTS NEEDING EVIDENCE:

FcRn Antagonists

B Cell Depletion – may provide remission

Complement Inhibitors

T and B Cell Inhibitors

Cytokine/Chemokine Inhibitors

My Approach to Treatment

- Baseline assessments
  - INCAT; R-ODS; Grip; TUG;
  - Manual Muscle Testing with MRC noting the muscles that are mildly weak

- Three-month trial of 1st Line Therapy
  - ICE trial -94% of those that responded did so at 2 months
  - Steroids- use a dose that you can be confident is high enough for success

- Reassess
  - Is there objective improvement? Continue for another 3 months
  - Did the patient get worse? Time to switch?
  - Stayed the same? Continue trial for another 3 months? Change dose?
  - Was there wear-off? Change dose or interval?

Factors Influencing Treatment Decisions

- Aggressive disease with significant functional deficits requires early response
  - IVIg is more likely than pulse steroids to provide early improvement
  - PLEx works at least as rapidly as IVIg
- Young patients not agreeable to cushingoid appearance
  - Pulse steroids rather than daily
  - IVIg induction
  - IV or SCIg maintenance
- Older patients have risks of osteoporosis, fractures, and diabetes, hypertension
  - IVIg may be more safe than steroids
  - But IVIg has increased risk for thrombotic events

Optimal Treatment of CIDP

- Looking for treatments that are safe, effective and are not a continuous burden to the patient and family
- No cure in sight
  - Still lacking pathophysiologic insights
- Treatments providing long-term remission are within reach
- Treatments that can control disease with minimal risk and inconvenience
  - Efgartigimod may meet this need
    - Shorter infusion time; less invasive than IVIg, PLEx or SCIg
    - Rapid reduction in IgG could provide a faster response than current treatments

Rationale to Target CIDP with Efgartigimod

Erik Hofman, PhD, Principal Scientist

Rationale to Target CIDP with Efgartigimod

Pathophysiology of CIDP

- Humoral and cellular immunity

Clinical evidence for pathogenic IgGs in CIDP

- Response rates with Ig-selective approaches

Preclinical evidence for pathogenic antibodies in CIDP

- Identification of nerve-reactive IgGs
- In vitro and passive transfer studies

Rationale to Target CIDP with Efgartigimod

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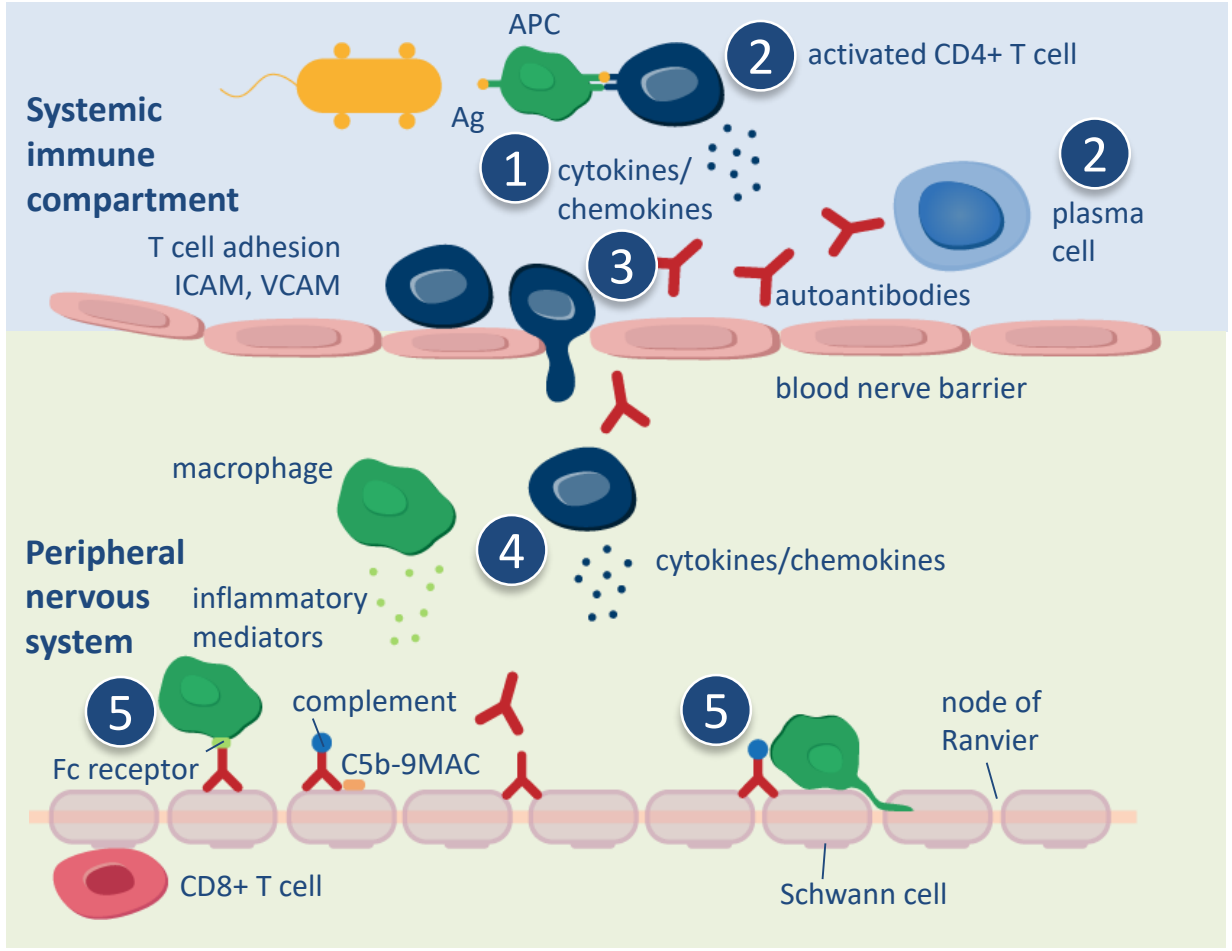
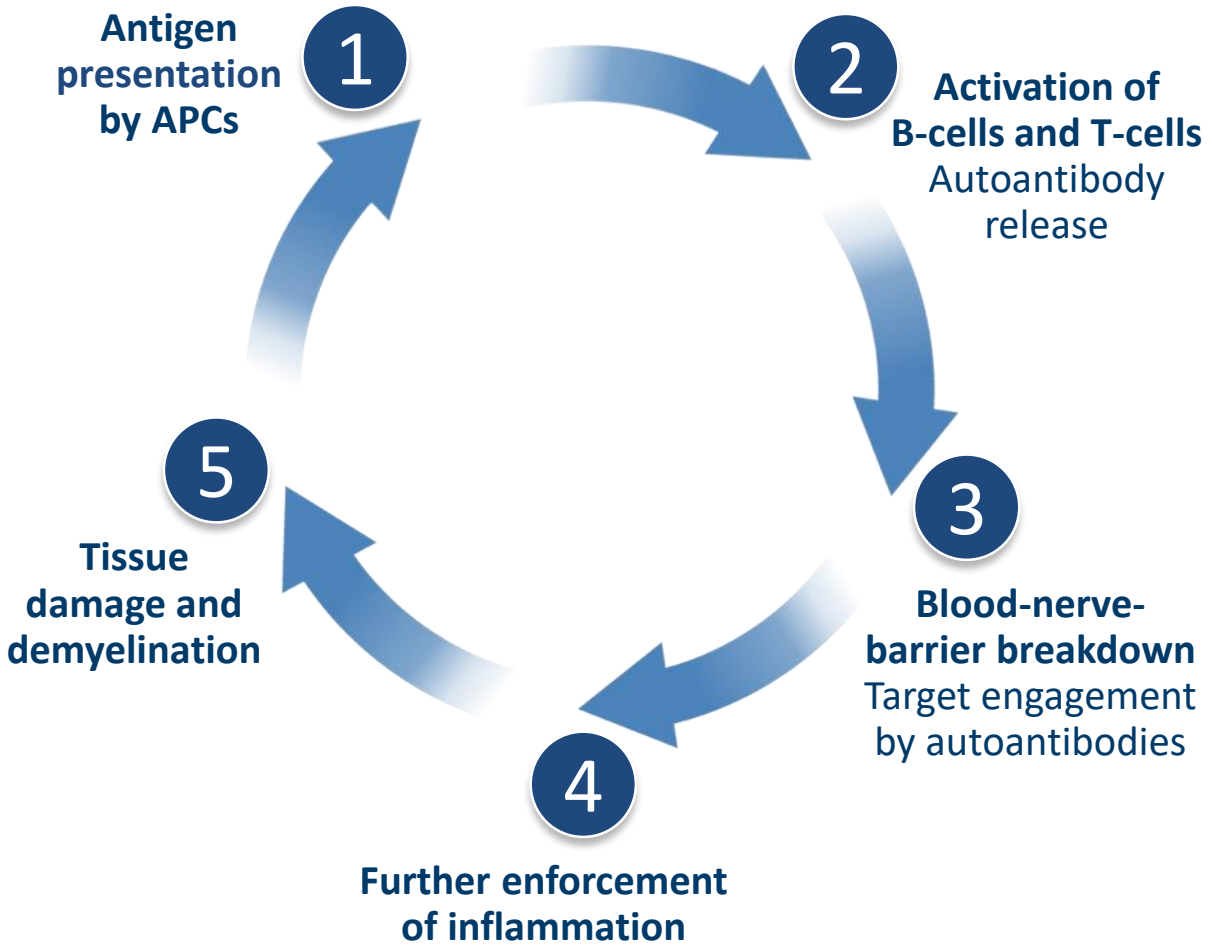
- In vitro and passive transfer studies

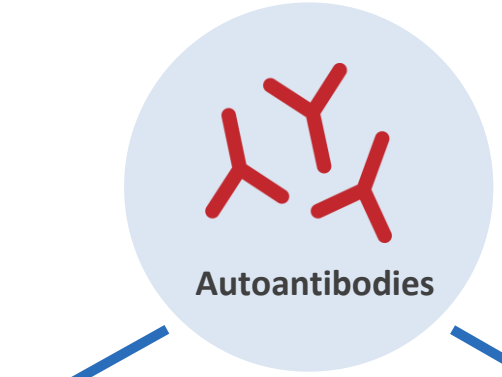
CIDP is an Autoimmune Disease Involving Both Cellular and Humoral Components of the Immune System



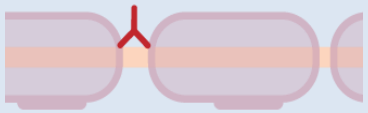


Mathey et al, 2015. J Neurol Neurosurg Psychiatry

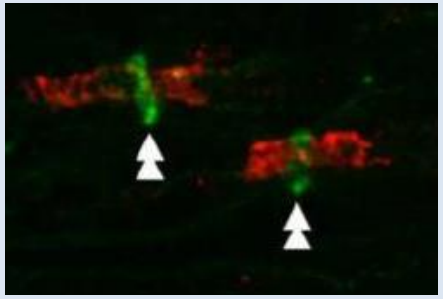
Autoantibodies: Central Mediators of CIDP Pathophysiology



1. Block nerve conduction



IgG detection on paranodal junction

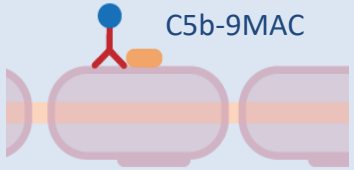


IgGs, Paranodal marker

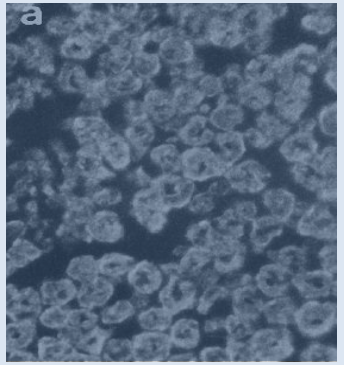
From: Manso et al, J Clin Invest. 2019 ;129(6):2222-2236

2. Activate complement

complement

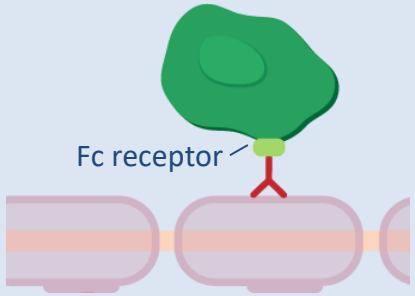


Complement deposition

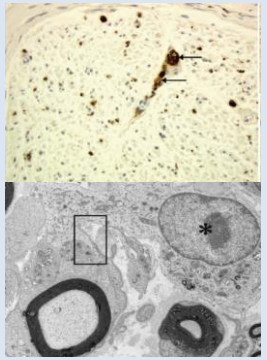


From: Mathey et al, J Neurol Neurosurg Psychiatry. 2015;86(9):973-85

3. Recruit macrophages



Macrophage infiltration



From: Sommer C, et al. Neurology. 2005 Dec 27;65(12):1924-9
Koike H, et al. Neurology. 2018 Dec 4;91(23):1051-1060

Rationale to Target CIDP with Efgartigimod

Pathophysiology of CIDP

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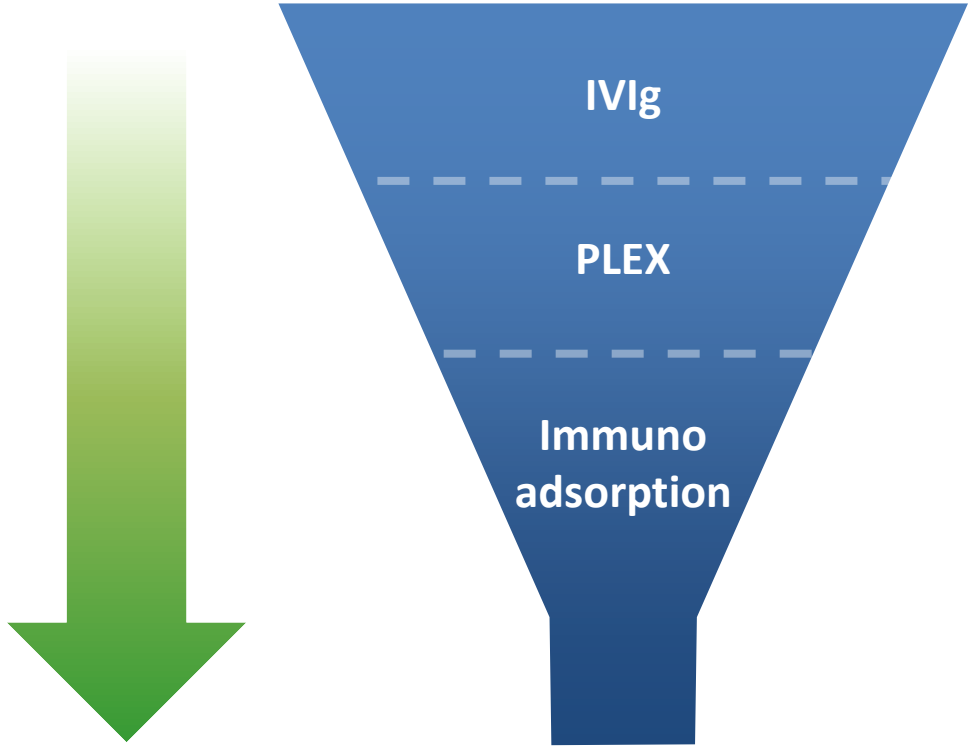
Increasing Selectivity for IgG Reductions Maintains Therapeutic Efficacy

Selectivity for IgG	MoA	Response rate
IVIg	Several/undefined MoA, including increased catabolism of IgGs	50-70%
PLEX	Removal of humoral serum factors	33-80%
Immuno adsorption	Immunoadsorption (IA) with tryptophan matrix: IgG, IgM, immune complex depletion	Comparable to PLEX
	IA with protein A: IgG depletion	80-100%



Clinical evidence for the role of pathogenic autoantibodies in CIDP

Oaklander et al (2017), Cochrane Database Syst Rev
Lieker et al (2017), J Clin Apher, 32(6):486-493
Zinman et al (2005) Transfus Apher Sci. 2005 Nov;33(3):317-24.

Plasma Exchange Observed to Be Highly Effective in CIDP

Study overview:

- 18 CIDP patients
- PLEX: non-selective washout of serum proteins
- 10 treatments over 4 weeks

Clear clinical improvement with PLEX and not with sham exchange

Outcome measures	Plasma exchange		Sham exchange		Significance †
	Before	After	Before	After	
Clinical measure:					
Neurological disability score Clinical grade	73.3 ± 5.3	**35.3 ± 4.5**	69.4 ± 6.4	71.1 ± 7.5	$p < 0.001$
Grip strength (kg)	4.6 ± 0.4	**3.0 ± 0.4**	4.3 ± 0.4	4.7 ± 0.5	$p < 0.001$
Electrophysiological measure:	15.8 ± 2.3	**28.5 ± 2.8**	15.1 ± 2.7	15.2 ± 3.1	$p < 0.003$
Σ proximal CMAP (mV)	7.3 ± 1.2	**11.0 ± 1.9**	7.1 ± 1.9	6.2 ± 1.4	$p < 0.01$
Σ distal CMAP (mV)	15.0 ± 2.0	**17.3 ± 2.6**	12.7 ± 2.3	12.2 ± 1.7	$p < 0.06$
Σ motor conduction velocity (m s^{-1})	91.3 ± 11.9	**104.5 ± 11.2**	86.7 ± 9.4	83.3 ± 9.9	$p < 0.006$
Σ distal motor latency (ms)	34.7 ± 5.5	**29.1 ± 2.9**	35.3 ± 4.7	37.7 ± 5.1	$p < 0.01$

Mean ± SD.; † *P* values were obtained from ANOVAs, repeated measures option, and refer to the differences between the effects of PE and SPE treatments.

Statistically significant improvement after PLEX indicates importance of humoral factors in CIDP

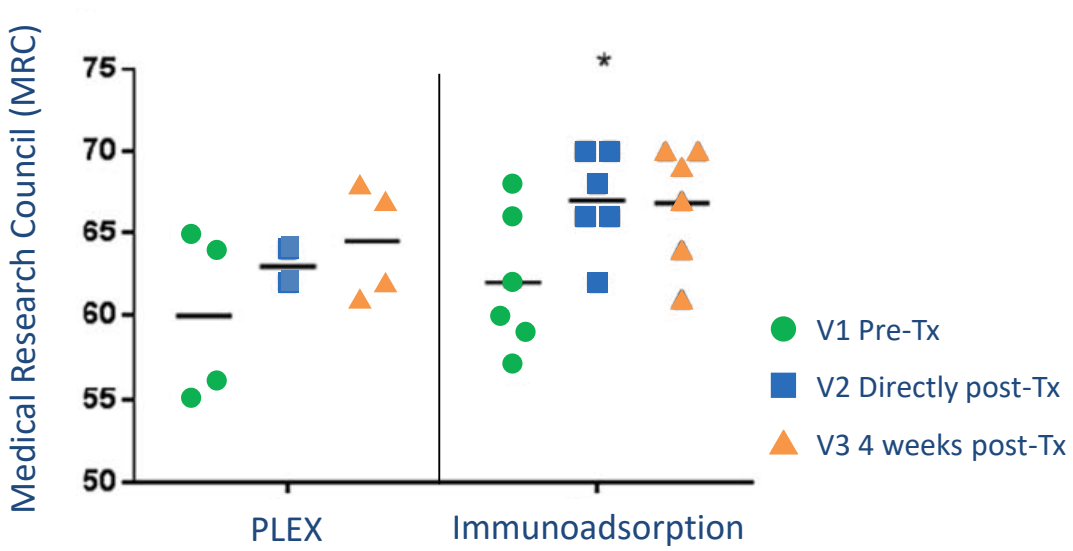
Hahn et al (1996), Brain, 119: 1055-1066

Tryptophan Immunoadsorption Comparable to PLEX in CIDP

Study overview:

- 18 CIDP patients
- IA with tryptophan removes IgG, IgM and immune complexes from circulation
- 6 treatments in 12 days
- Clinical scores used: MRC and INCAT (not shown)

Clear clinical improvement using PLEX and IA



Treatment	Responders N (%)
PLEX	4/9 (44.4)
IA	6/9 (66.7)

Selective depletion of IgGs with tryptophan IA observed to be at least as effective as PLEX

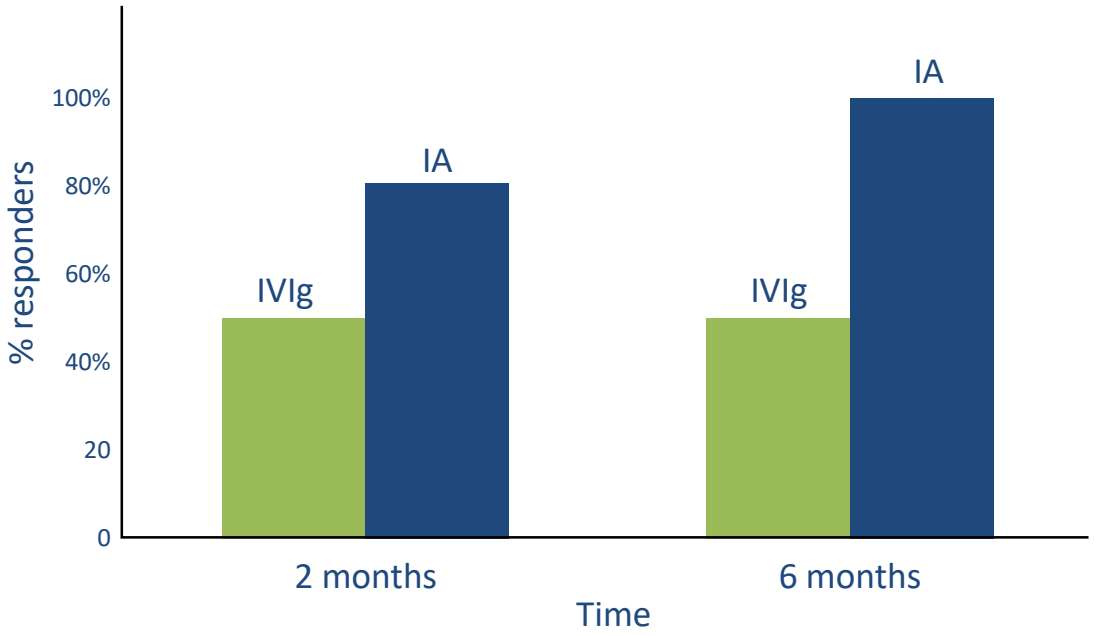
Lieker et al (2017), J Clin Apher, 32(6):486-493

Protein A Immunoadsorption Comparable to IVIg in CIDP

Study overview:

- 13 CIDP patients
- IA with protein A: highly selective for IgG
- Monthly treatment for 6 months
- Responders: stabilization or improvement in at least 2/4 clinical measures without deterioration in the other measures.

Superior clinical response rate observed in IA over IVIg



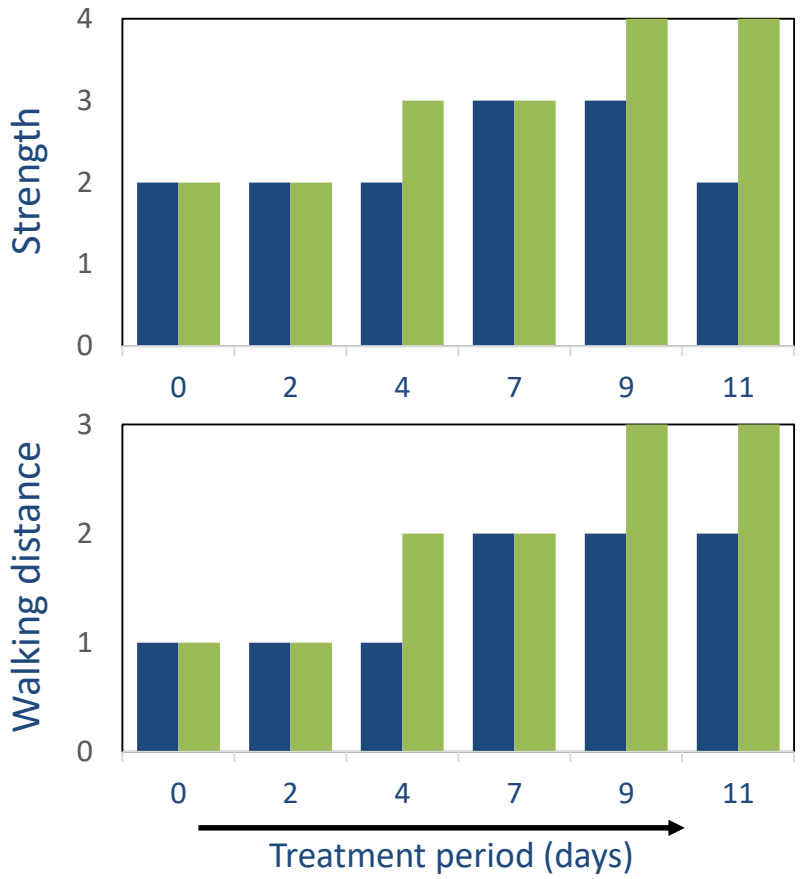
Mode of action of efgartigimod most comparable to IA selectively addressing IgGs

Zinman et al (2005) Transfus Apher Sci. 2005 Nov;33(3):317-24.

Protein A Immunoadsorption Comparable to PLEX in CIDP

Case study:

- Patient responsive to PLEX
- PLEX replaced by repeated cycles of IA
- IgG levels reduced from 6.9 to 1.6 g/L
- Effect on motor function tested on two scales



Applied Scaling of Disability

Walking distance (0–4)	Strength (0–5)
1 Ability to stand	1 Muscle tension without movement
2 Ability to walk <5m	2 Slight movement
3 Ability to walk 5–100 m	3 Movement against resistance
4 Ability to walk freely	4 Weakness
	5 Normal

CIDP patients can benefit from repeated IgG removal using IA

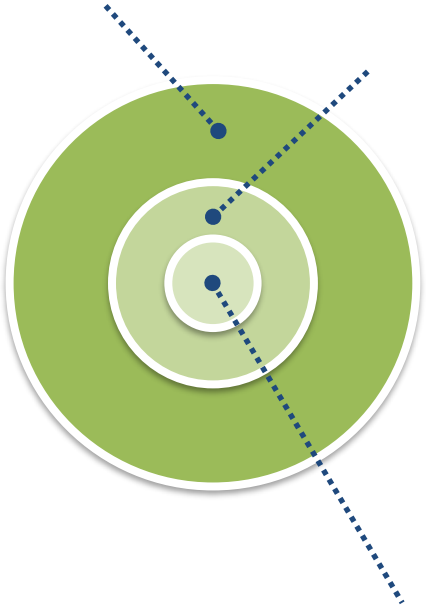
Ullrich et al (1998), Transfus Sci 19:33-38

Agenda

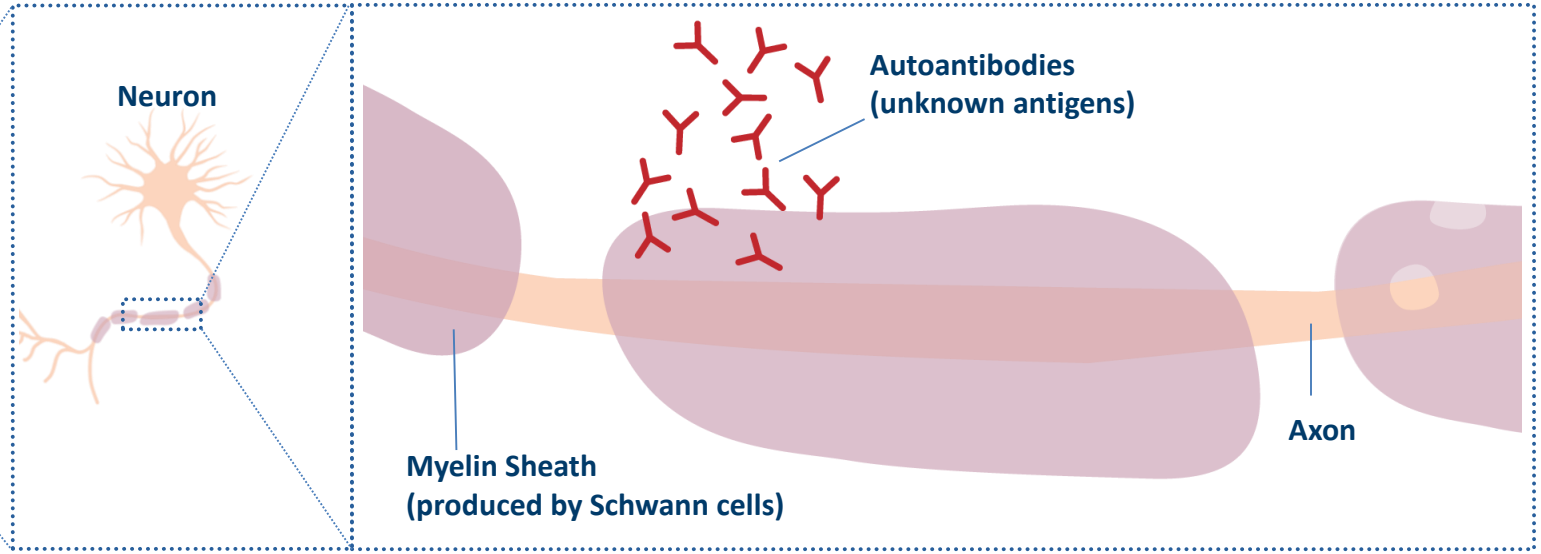
- Pathophysiology of CIDP
  - Humoral and cellular immunity
- Clinical evidence for pathogenic IgGs in CIDP
  - Response rates with Ig-selective approaches
- **Preclinical evidence for pathogenic antibodies in CIDP**
  - Identification of nerve-reactive IgGs
  - In vitro and passive transfer studies

Direct Evidence for Autoantibodies in CIDP: Current Status

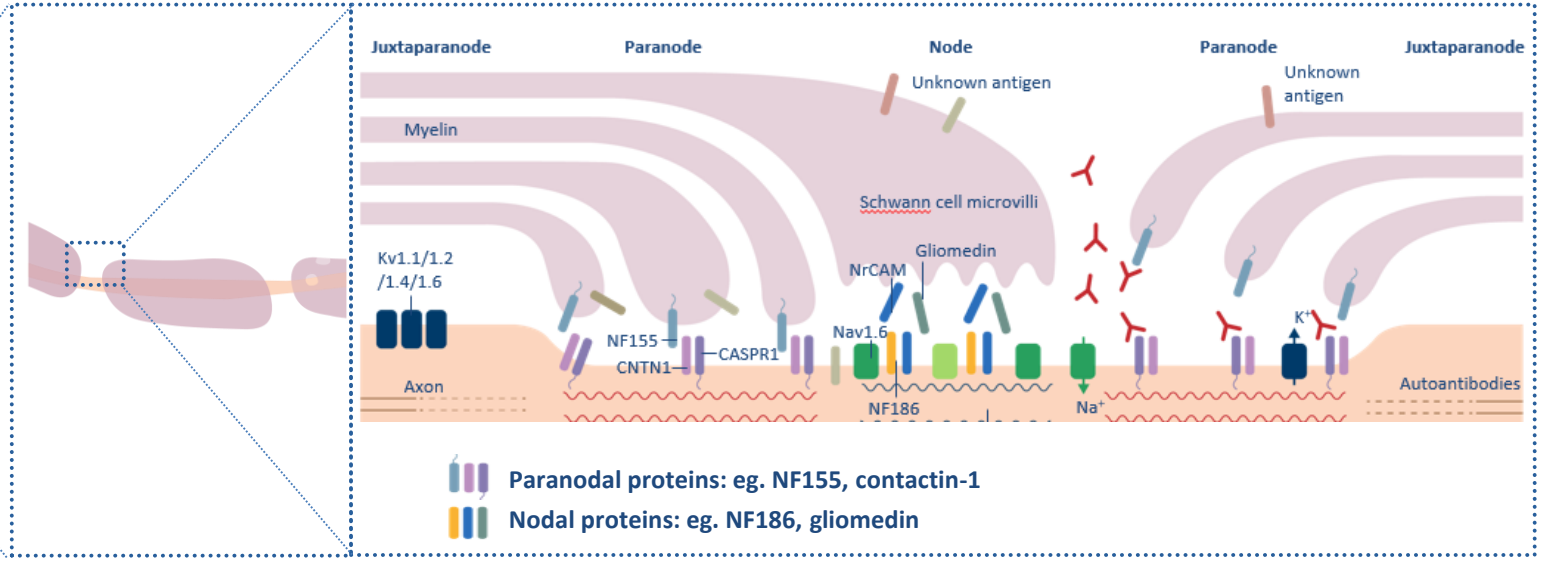
No autoantibodies identified (60-70% of patients)



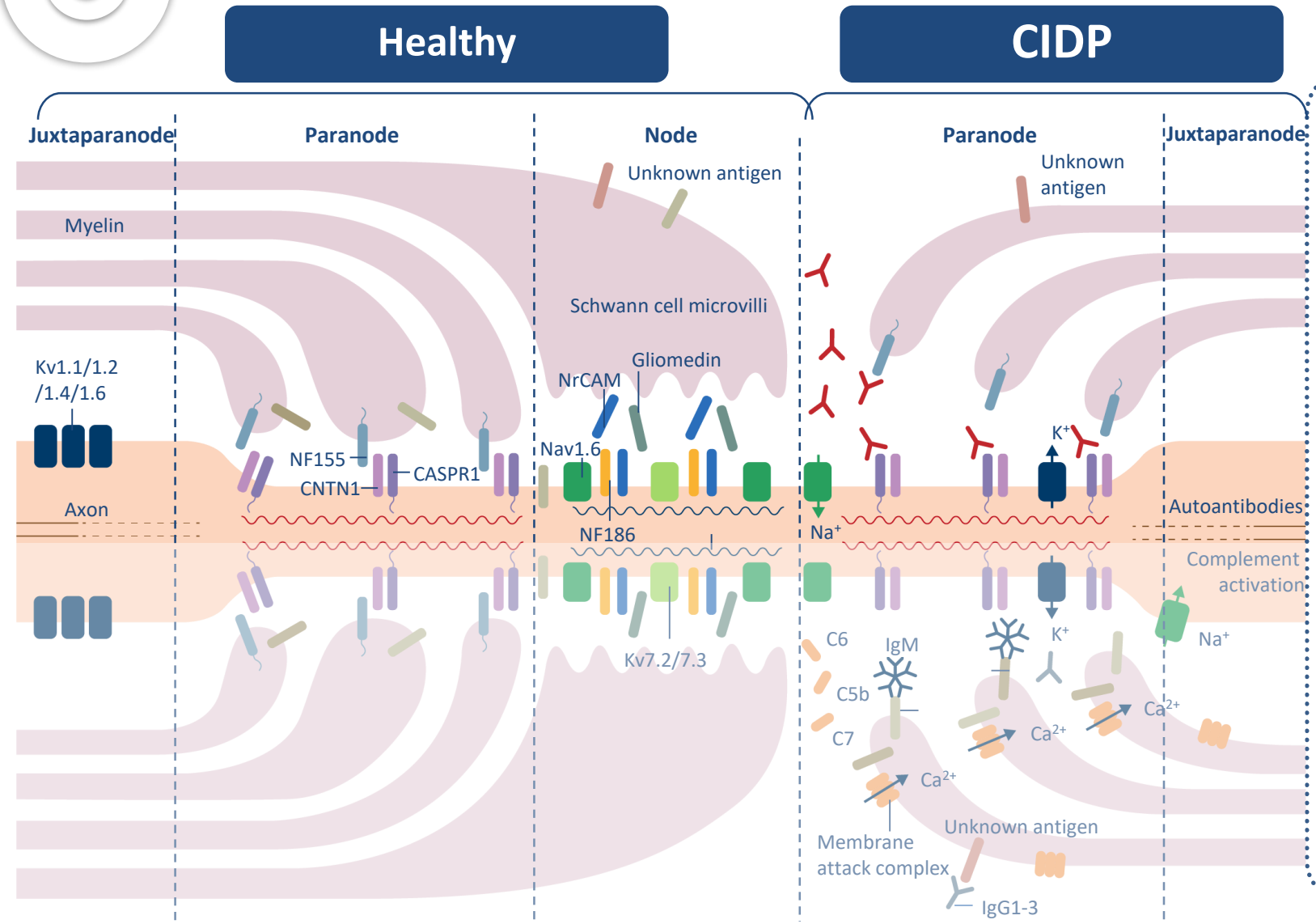
Anti-myelinated peripheral nerve IgG (30-40% of patients)



Anti-paranodal IgG4 (~10% of patients)



Autoantibodies to Paranodal Junction Found in CIDP



Paranodal junction consists of NF-155, CNTN1, Caspr1

- Docking of myelin to axon
- Maintaining functional segmentation

Autoantibodies found in CIDP:

- Targeting NF-155, Caspr1, CNTN1
- IgG4

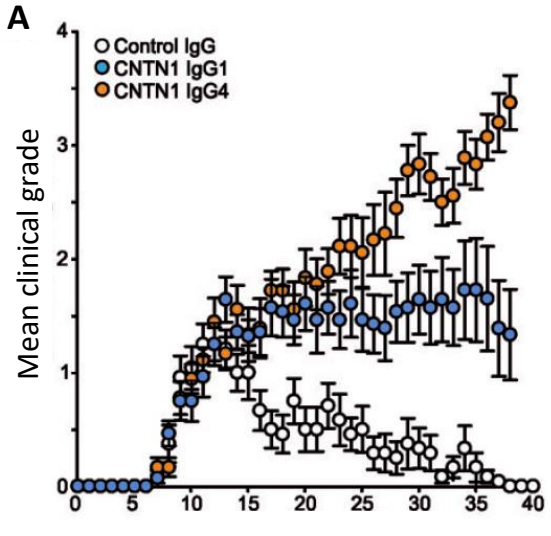
Titers correlated with disease severity

Macrophage or complement involvement minimal

Querol et al (2017) Nature Rev Neurol 13:533-547

Autoantibodies to Paranodal Junction Are Pathogenic in Passive Autoimmune Neuropathy Transfer Model

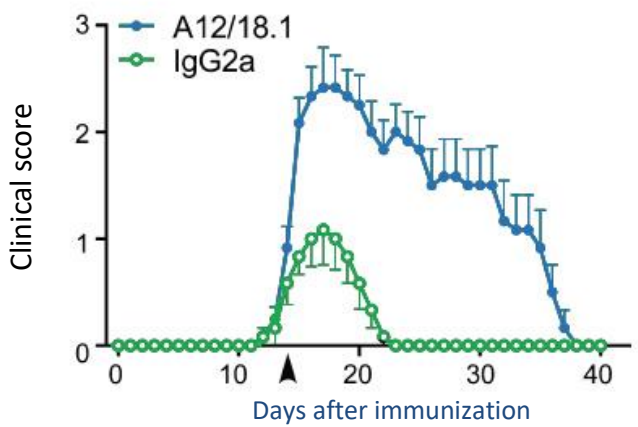
EAN model + anti-CNTN1 IgGs



P2 myelin peptide (50 µg)

Purified IgGs (500 µg)

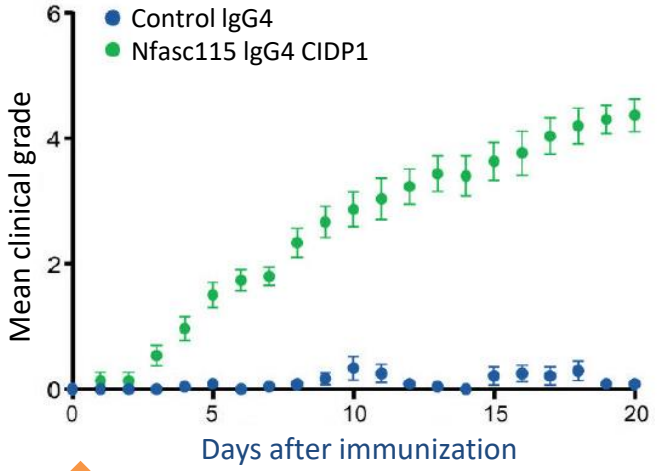
EAN model + anti-neurofascin IgG



P2 myelin peptide (50 µg)

Anti-pan neurofascin mIgG2a

Intrathecal injection of NF-155 IgG4 from CIDP patient in healthy Lewis rats



Anti-NF155 IgG4

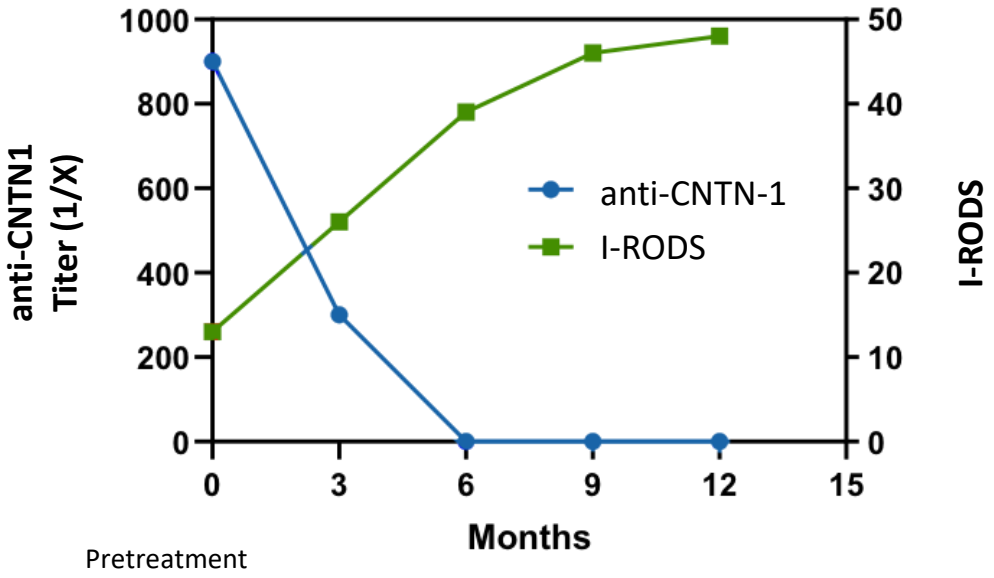
Manso et al (2016), Brain 139: 1700–1712

Ng et al (2012), Neurology 79: 2241-2248

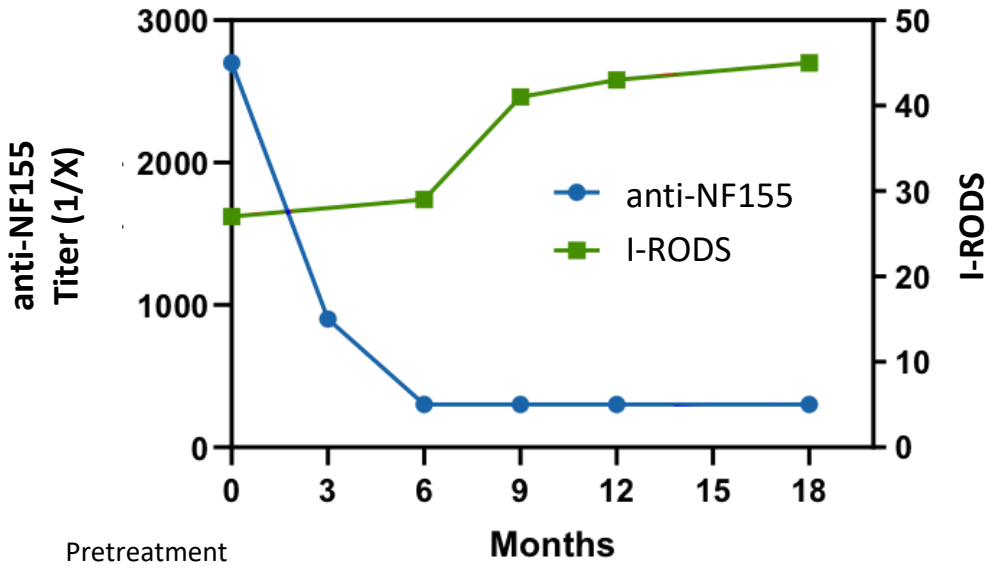
Manso et al (2019), J Clin Invest. 129(6):2222-2236

Autoantibody Levels to Paranodal Junction Correlate with Disease Severity

Patient 1: anti-CNTN-1 vs I-RODS



Patient 2: anti-NF155 vs I-RODS



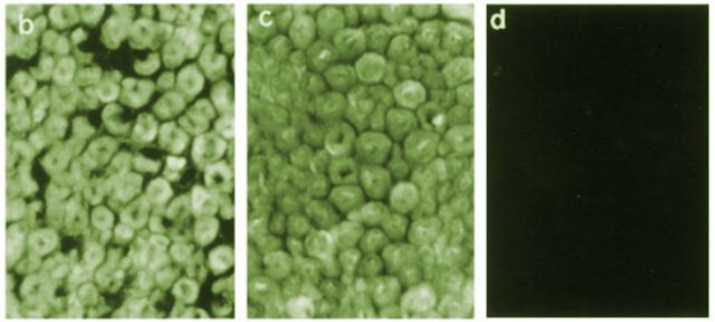
Decreasing anti-paranodal IgG titers lead to clinical improvement on outcome measures

Adapted from: Querol et al (2015), Neuroimmunol Neuroinflamm 2015;2:e149

Autoantibodies to Myelinated Peripheral Nerves Are Found in a Significant Part of the CIDP Population

Rat sciatic nerve

IgG, patient serum | IgG, patient pur. IgG | IgG, control serum



33% of CIDP patients have IgGs binding to myelinated nerves

Mouse teased sciatic nerves

CIDP serum IgG | Nodal marker

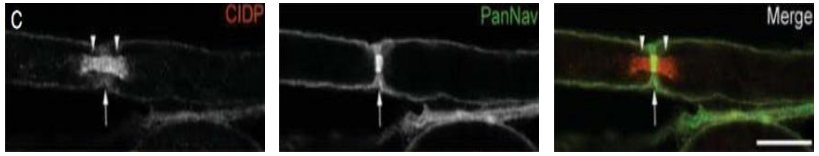


Table 1. Percentage of sera that bound axonal compartments.

Percentage of sera that stained	NC	CIDP	OND
Node	0	20 (12)†	3.8 (3)
Paranode	0	18 (8)†	0
Any compartments	0	30	3.8

OND: other neurological disorders

30% of tested CIDP sera bind to compartment of myelinated nerves

Cultured Schwann cells

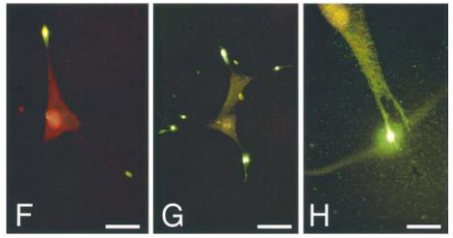


Table 1 Anti-Schwann cell IgG immunofluorescence

Serum group	Positive
GBS	24% (56 out of 233)
CIDP	26% (12 out of 46)
Healthy donor pool	
Single healthy donors	6% (2 out of 34)
Purified IV g	0% (0 out of 3)
HMSN type 1	0% (0 out of 47)
Alzheimer's disease	0% (0 out of 4)

26% of tested CIDP sera have IgGs binding to cultured Schwann cells

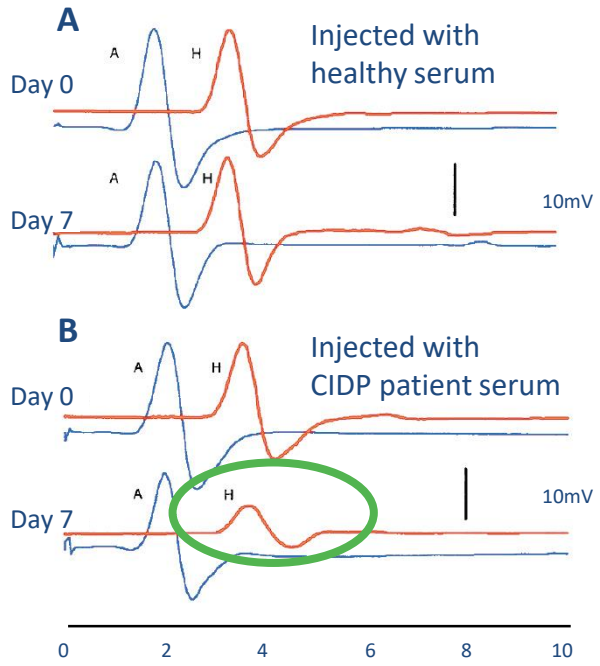
Yan et al (2000), Ann Neurol, 47(6): 765-775

Devaux et al, 2012. J Per Nerv Syst

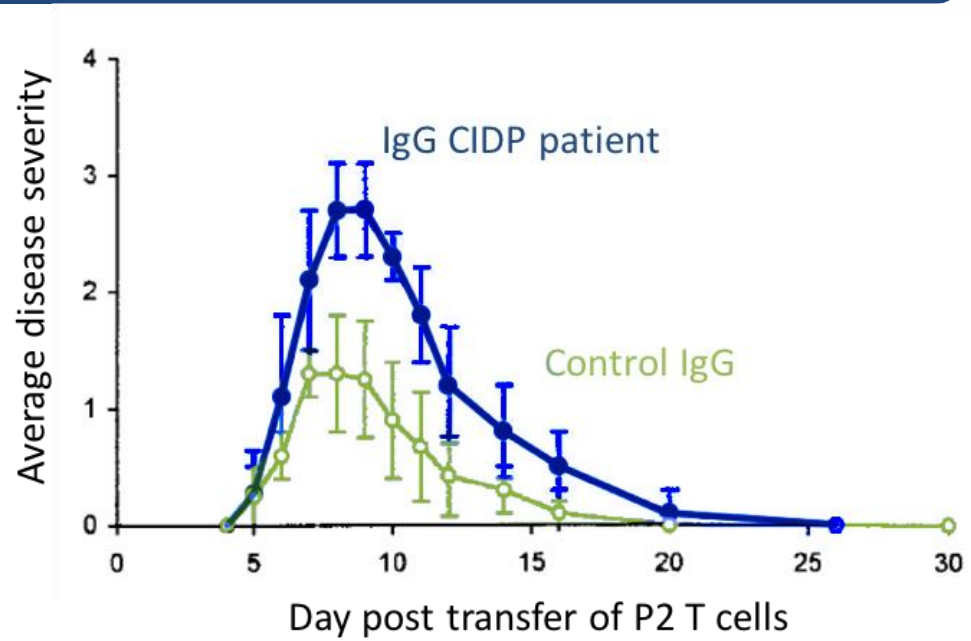
Kwa et al, 2003. Brain 126:361-375

Autoantibodies to Myelinated Peripheral Nerves Are Pathogenic in Passive Transfer Animal Models

Intraneural injection of CIDP IgGs causes conduction block and demyelination



Exacerbation of EAN disease model by injection of CIDP IgG



Autoantibodies against components of myelinated nerve fiber can cause conduction block and disease exacerbation upon passive transfer to animal models

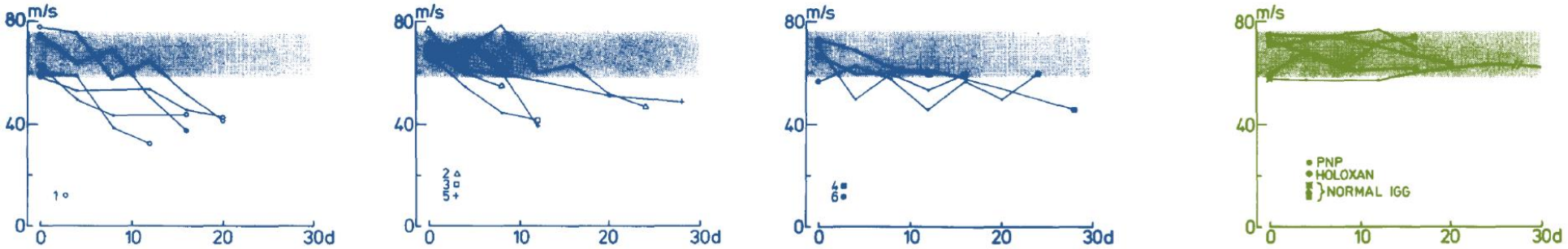
Yan et al (2000), Ann Neurol, 47(6): 765-775

IgGs Isolated from Unselected CIDP Patients Can Reduce Nerve Conduction Speed in Non-human Primates

- 6 CIDP patients with good response to PLEX
- Crude Ig or purified IgG from patients injected (IM or SC) in non-human primates
- Nerve conduction velocities measured in sciatic nerves at regular time points

CIDP IgG | **Other IgG**

Nerve conduction speed



Time after injection (days)

- Clear reduction in nerve conduction speed after transfer of CIDP IgGs
- Not observed with IgG from healthy subjects or non-related indications

Heiniger et al (1984), J Neurol Sci 66:1-14

Conclusions

CIDP: Humoral and cellular immunity involved

Clinical response is maintained using treatments with increasing selectivity for IgGs

Nerve-reactive IgGs have been found in CIDP patients

In vitro and passive transfer studies show the pathogenic potential of these IgGs

IgGs play a key role in the pathogenesis of CIDP

Clear rationale for FcRn inhibition (and IgG reduction) with efgartigimod in CIDP

Phase 2 ADHERE Trial Design of Efgartigimod in CIDP

Wim Parys, M.D., CMO

Objectives of Phase 2 ADHERE Study

- Investigate **clinical efficacy** of ENHANZE® efgartigimod SC in CIDP compared to placebo
- Assess long-term **safety and tolerability** of ENHANZE® efgartigimod SC in CIDP
- Evaluate additional **PROs** including patient-reported QoL and satisfaction with treatment
- Determine **PK, PD** and **immunogenicity** of ENHANZE® efgartigimod SC with chronic dosing
- Evaluate **biomarkers** of CIDP disease activity

Key Design Considerations for Phase 2 ADHERE Study Population

adhere chronic inflammatory demyelinating polyneuropathy study

argenx

Increase accuracy of diagnosis	• Typical and atypical CIDP patients (except sensory CIDP) • EFNS/PNS criteria • Adjudication committee of experts
Show disease activity	• Observation period after therapy stop • Newly diagnosed
Limit confounding factors	• Washout period with IVIg/SCIg/Corticosteroids • Other immunosuppressants excluded • Treatment naive patients included
Assess role of IgG auto-ab	• Open label treatment with efgartigimod to determine responders

Phase 2 ADHERE Study Design

adhere chronic inflammatory demyelinating polyneuropathy study

argenx

Identify patients with active CIDP

Confirm IgG autoantibody involvement

Document efficacy & safety efgartigimod vs placebo

Treatment period

Open label

Placebo-controlled

Screening	Run-in period	Stage A	Stage B (stage A responders only)
• Confirmation of diagnosis by independent committee	• Worsening of disease within 12 weeks after drug withdrawal (INCAT, I-RODS, grip strength) • Newly diagnosed/treatment naïve skip Run-in period	Efgartigimod weekly SC	Placebo weekly SC Efgartigimod weekly SC
≤4weeks	≤13weeks	Up to 12 weeks, until clinical improvement (ECI)	Up to 48 weeks

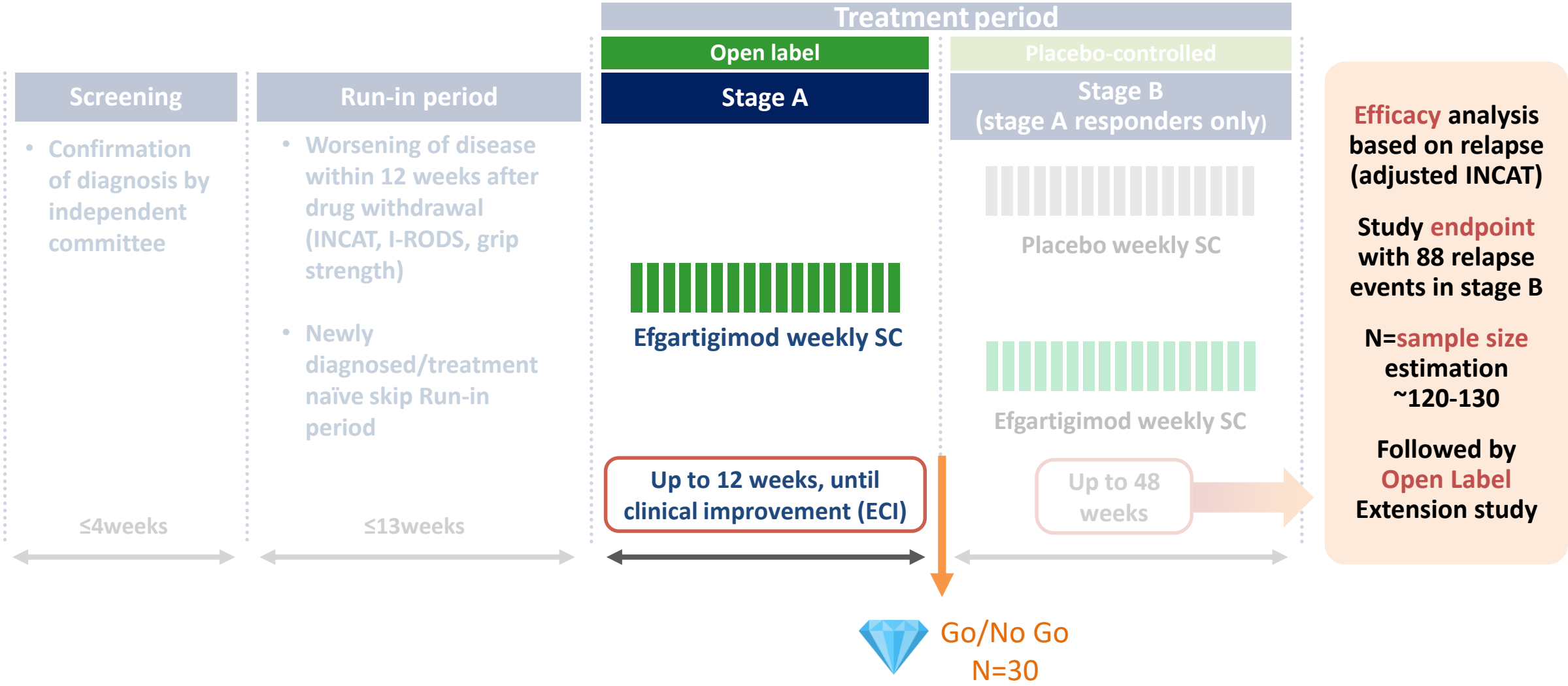
Efficacy analysis based on relapse (adjusted INCAT)

Study **endpoint** with 88 relapse events in stage B

N=**sample size** estimation ~120-130

Followed by **Open Label** Extension study

GO/NO Decision During ADHERE Study



ADHERE Study Relies on Established Clinical and Regulatory Endpoints

Primary endpoint of Stage B

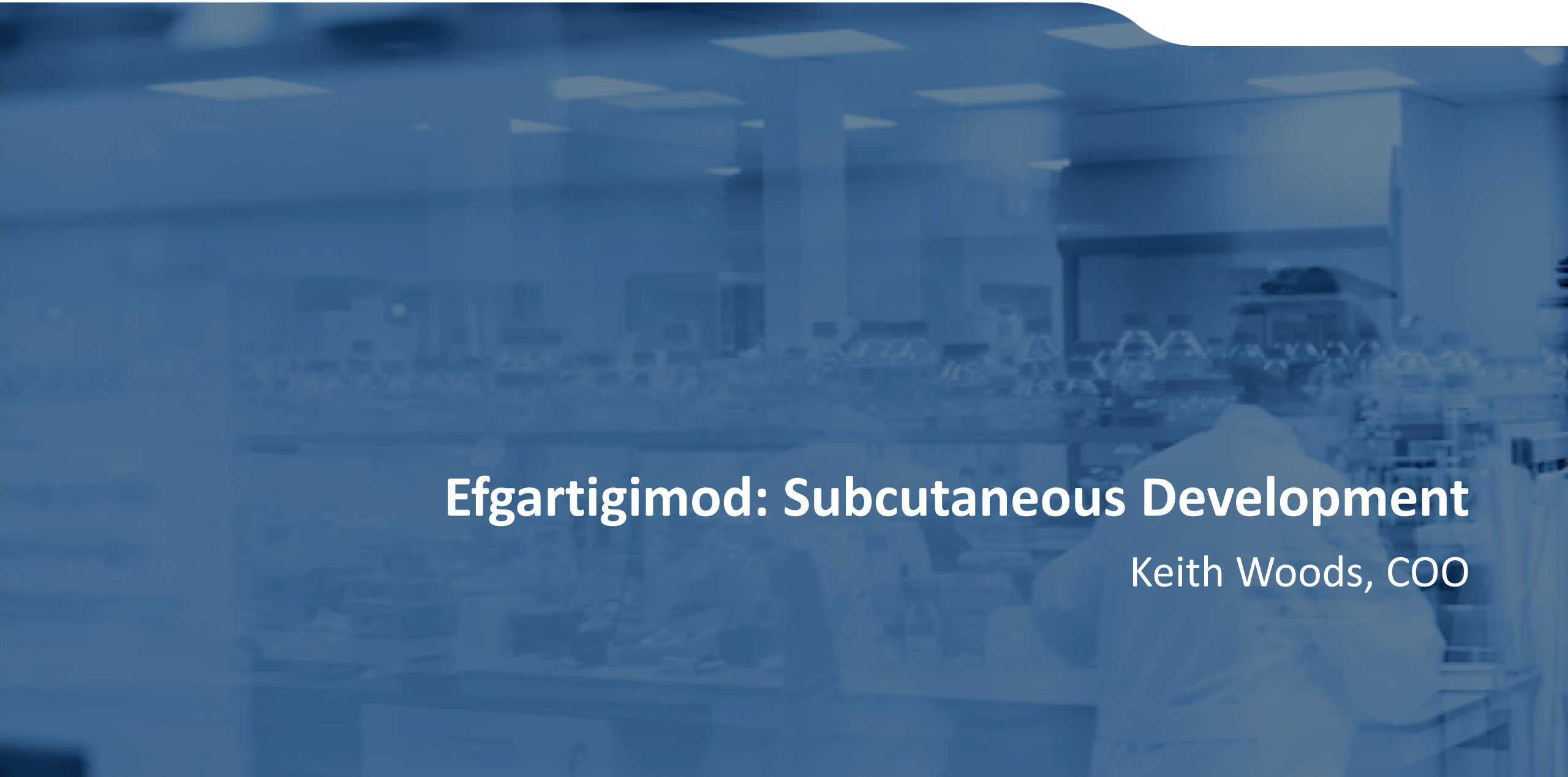
- Time to first INCAT deterioration compared to Stage B baseline

Secondary endpoints of Stage B

- Clinical efficacy as determined on established clinical measures:
  - MRC Sum score
  - I-RODS disability score
  - TUG score
  - Mean grip strength assessed by Martin vigorimeter
- Safety
- PK/PD and immunogenicity

Exploratory endpoints

- Autoantibody levels against paranodal proteins and myelinated nerves: change over time during Stage A and B
- Patient reported outcomes



Efgartigimod: Subcutaneous Development

Keith Woods, COO

Global Collaboration and License Agreement for ENHANZE® Drug Delivery Technology

- $30M upfront payment and $10M to exercise additional targets; third target still to be named
- Exclusive access to FcRn and C2; no other FcRn-targeting agent can employ ENHANZE® technology
- Up to $160M in milestone payments per target
- Mid-single digit royalties on marketed product sales

ENHANZE® Is a Unique "Volume Enabler"

~2mL is maximum volume subcutaneous space can accommodate in 1 push

How do you solve for this?

Effective FcRn blockade requires >2mL volume regardless of modality

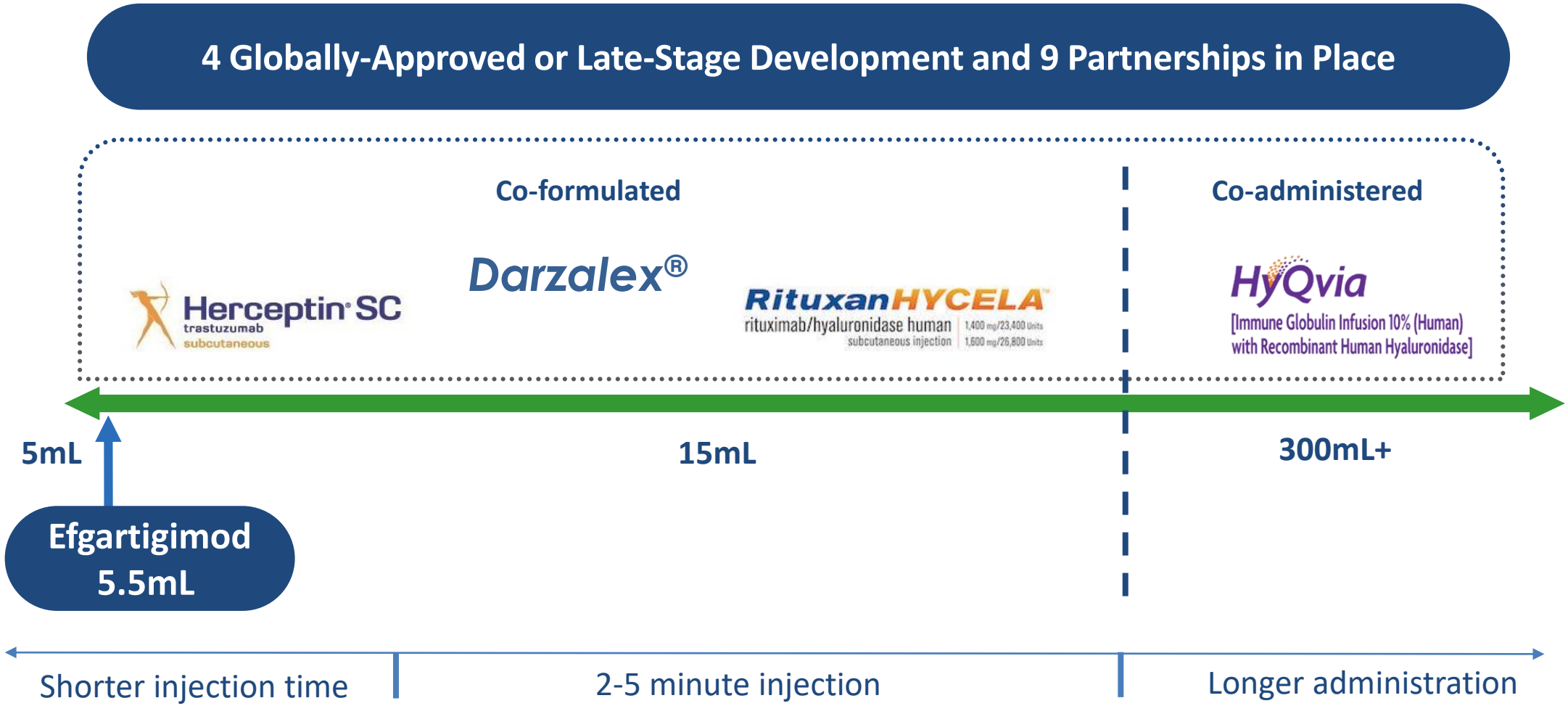
ENHANZE® enables single subcutaneous injection of >2mL

ENHANZE® Drug Delivery Technology Offers Optionality to Patients

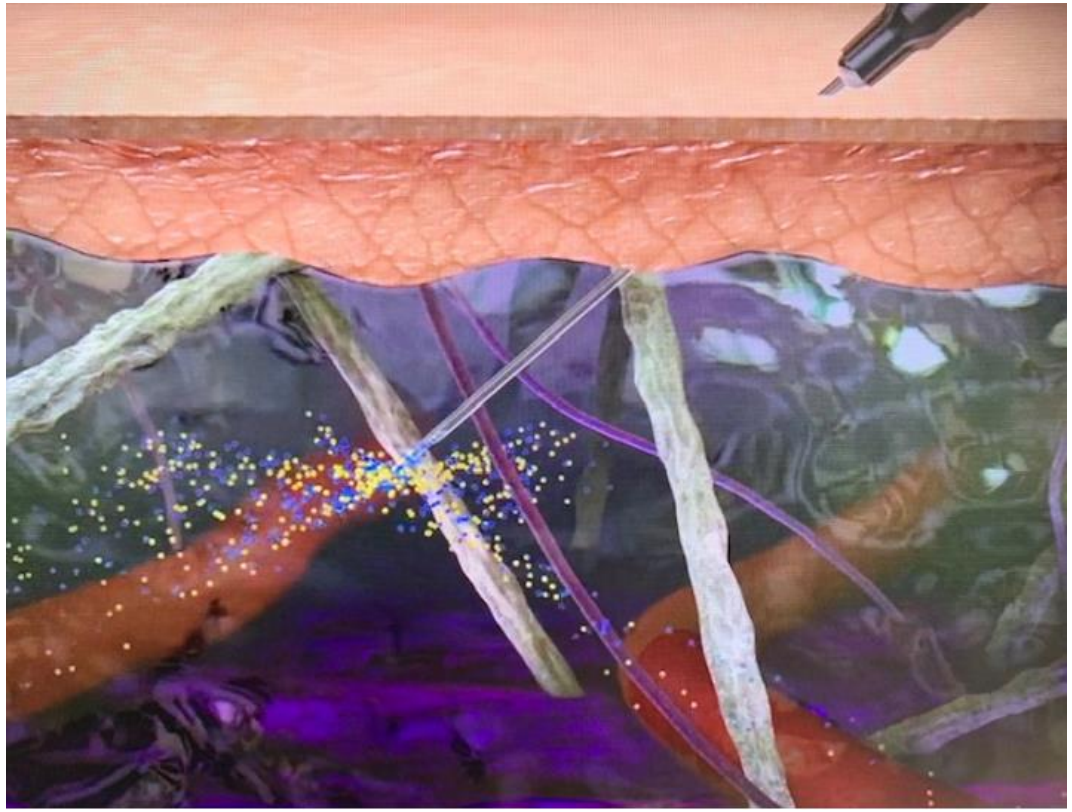
Drug material from IV infusion…	…into single subcutaneous injection
• Hospital/clinic or infusion service	• At-home convenience
• Administered by HCP	• Self-administered
• Weight-based infusion	• Flat dose single injection
• ≤60 minutes	• As fast as 1 minute

No premedication needed

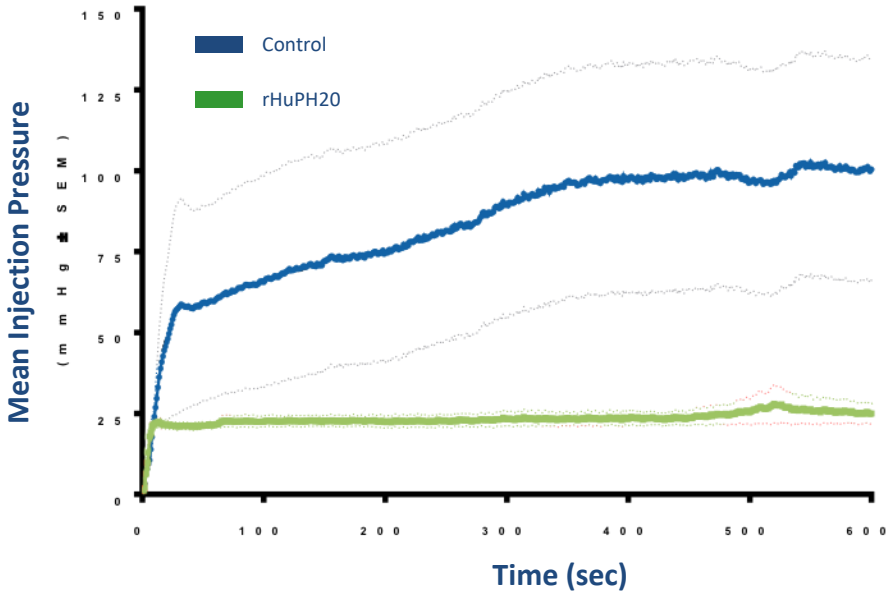
Commercially-Validated ENHANZE® Drug Delivery Technology



ENHANZE® Clears Path for Subcutaneous Injection; Reduces Back Pressure



SC Injection Pressures

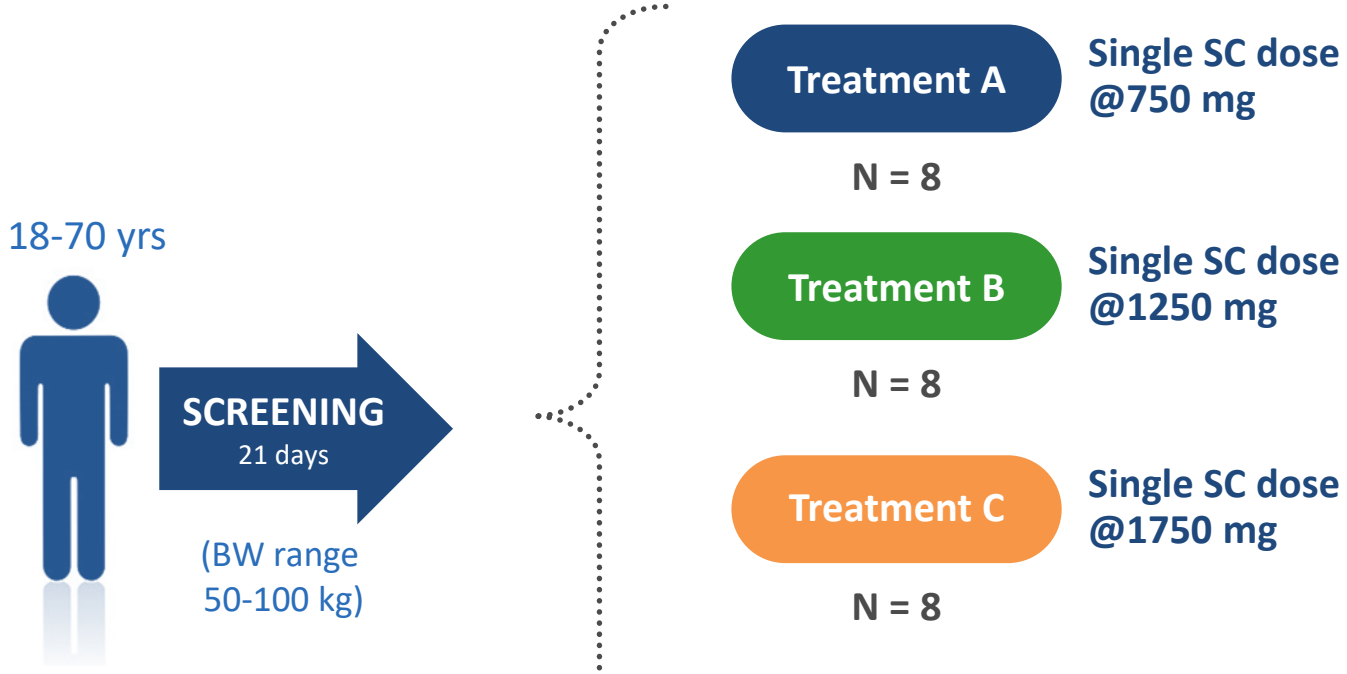


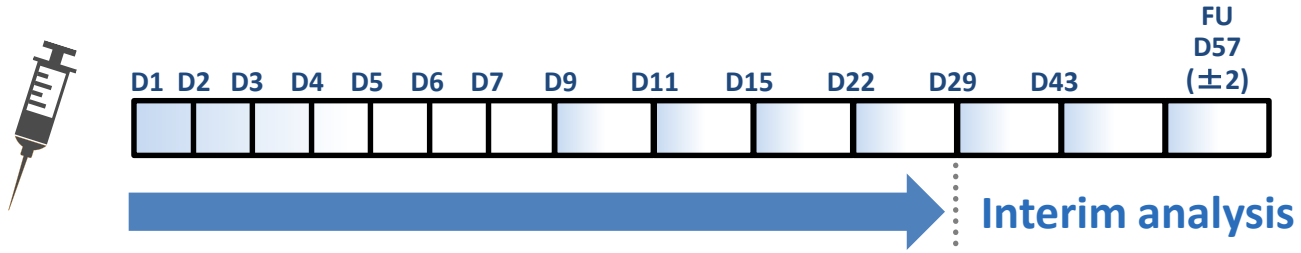
Significantly higher injection pressure without ENHANZE®

Reduced injection pressure with ENHANZE®

ENHANZE® permits rapid administration of larger volumes SC and can reduce frequency of administration

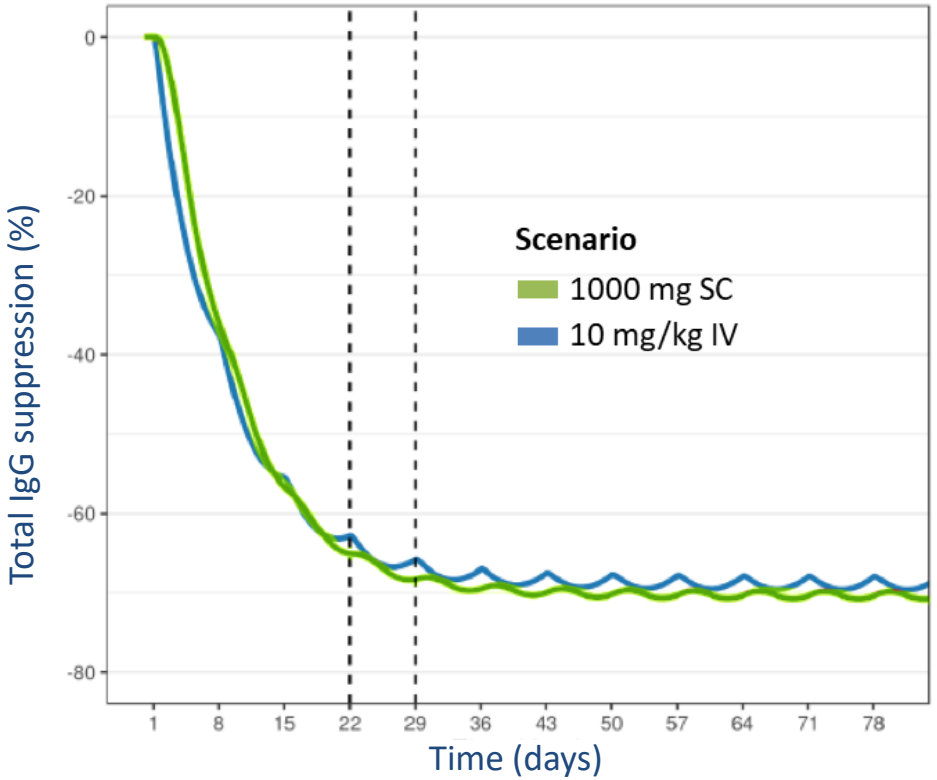
Phase 1 HV Study Trial Evaluated Multiple Dose Levels of ENHANZE® Efgartigimod SC Formulation



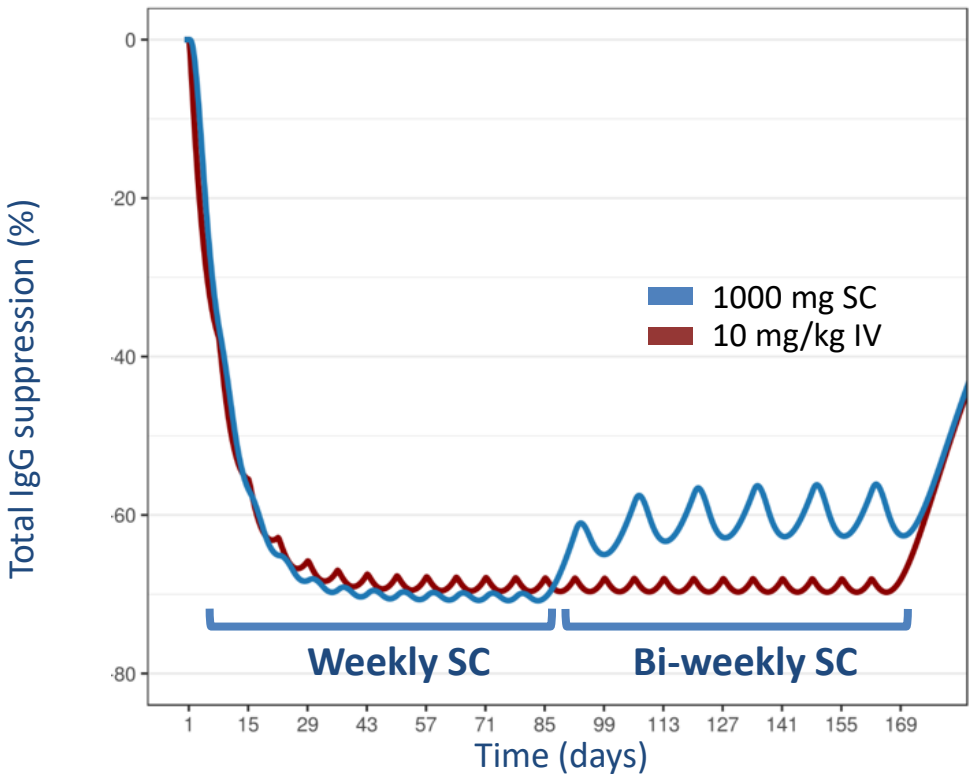


ENHANZE® Efgartigimod SC Formulation Retains PD Profile of IV Efgartigimod

Weekly dosing: 1000mg SC = 10mg/kg IV

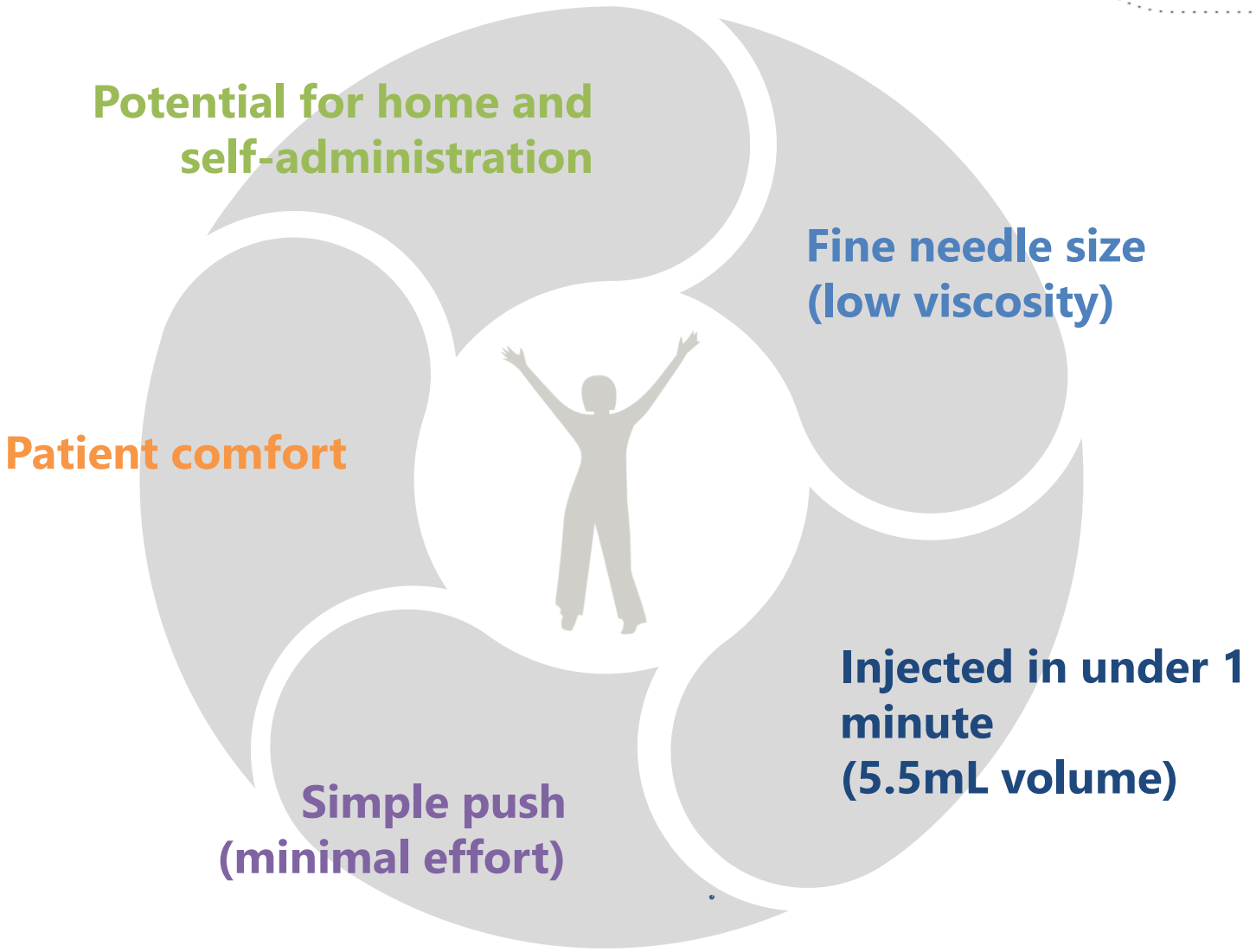


Model suggests potential for bi-weekly dosing



ENHANZE® efgartigimod SC was well-tolerated; adverse events were mild and transient

ENHANZE® Efgartigimod SC Formulation Aims to Patient Experience



Advancing ENHANZE® Efgartigimod SC into Development Pipeline

IV Efgartigimod

adapt myasthenia gravis study

advance immune thrombocytopenia study

ENHANZE® SC Efgartigimod

adhere chronic inflammatory demyelinating polyneuropathy study

Bridging strategy in MG indication

IV Efgartigimod + SC Efgartigimod

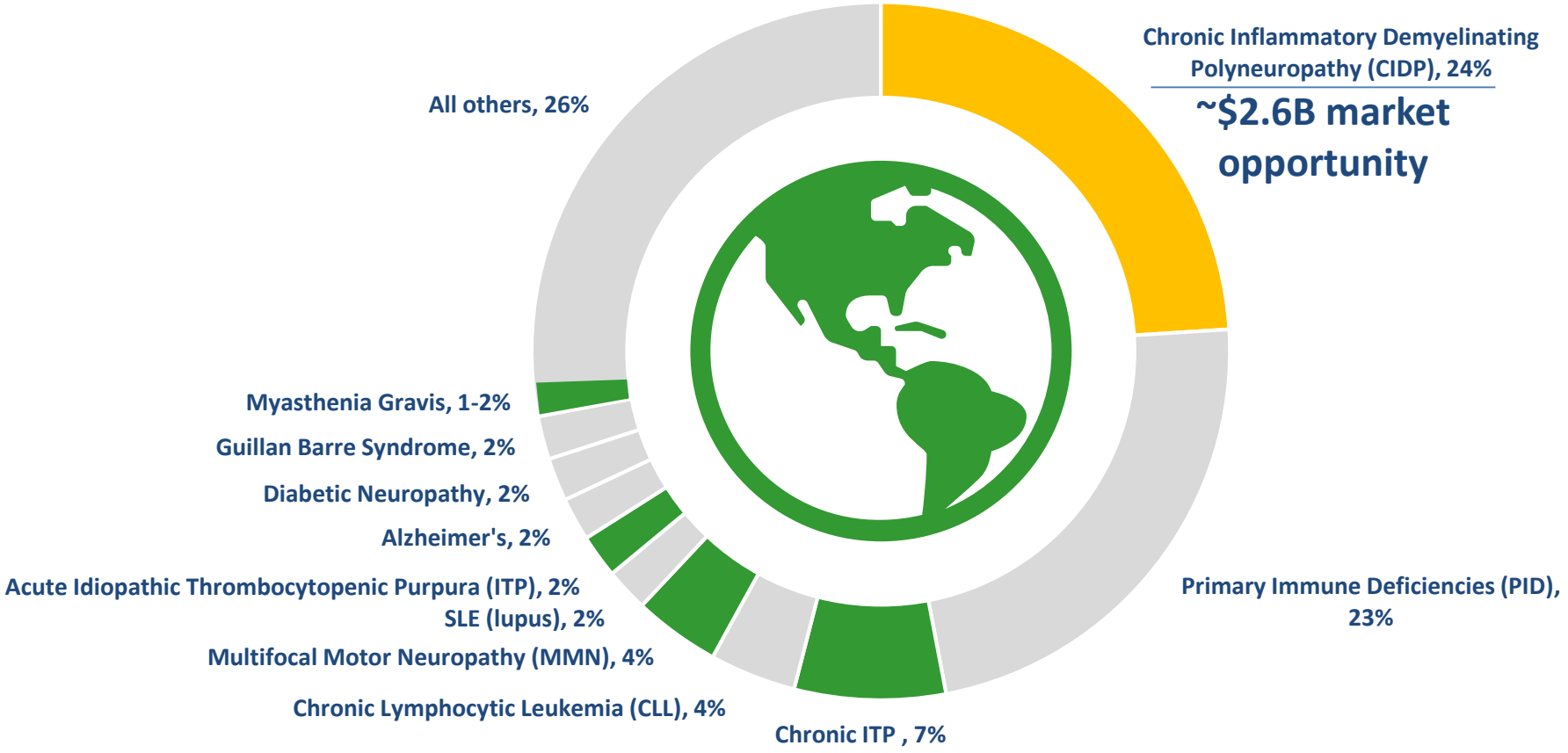
2nd Phase 3 in ITP

Future registrational trials can incorporate IV and SC strategy at onset

CIDP is a ~$2.6B market opportunity

Expected to grow double digit per year

Total IVIg market $11.1 Bn; 9% CAGR



MDSAS: Immunoglobulin Database Report 2015/16, CSL

Q & A

Thank You