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Welcome and Introduction
Tim Van Hauwermeiren, CEO

Chronic Inflammatory Demyelinating Polyneuropathy
Treatment challenges and high medical unmet need
Dr. Richard Lewis, M.D., Cedars-Sinai Medical Center

Rationale to Target CIDP with Efgartigimod
Erik Hofman, Ph.D., Principal Scientist

Phase 2 ADHERE Trial Design of Efgartigimod in CIDP
Wim Parys, M.D. CMO

Efgartigimod: Subcutaneous Development
Keith Woods, COO

Q&A

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

Efgartigimod: Pipeline-in-a-Product Opportunity
Clinical proof-of-concept achieved for neuromuscular and hematology indications

Landscape of IgG-mediated severe autoimmune diseases (sampling)

- Epidermolysis Bullosa Acquisita
- Immune Thrombocytopenia
- Scleroderma
- Lupus
- Myasthenia Gravis
- Multiple Sclerosis
- Rheumatoid Arthritis
- Anca Vasculitis
- Pemphigus
- Bullous Pemphigoid
- Bullous Pemphigoid
- Multiple Sclerosis
- Anca Vasculitis

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
Neuromuscular 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

**Standalone Products (Built to be Interchangeable)**

- **IV Efgartigimod**
  - 10 mg/kg
  - 60-minute infusion

- **ENHANZE® Efgartigimod SC**
  - 10 mg/kg
  - Subcutaneous injection

- **IV Efgartigimod + SC Efgartigimod**
  - 10 mg/kg + 330 mg fixed (2ml)
  - IV infusion induction
  - SC injection maintenance

**ADVANCE SC Trial**

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
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.

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

#### Upper Extremity

- **0**: No upper limb problems
- **1**: Symptoms in 1 or both arms; not affecting ability to perform any of the following: zippers, buttons, washing or brushing hair, using knife and fork together, handling small coins
- **2**: Symptoms in 1 or both arms affecting but not preventing any of functions listed above
- **3**: Symptoms in 1 or both arms preventing 1 or 2 functions
- **4**: Preventing 3 or more functions but some purposeful movements
- **5**: Inability to use either arm for any purposeful movement

#### Lower Extremity

- **0**: Walking not affected
- **1**: Walking affected but walks independently outdoors
- **2**: Usually uses unilateral support (stick, single crutch, 1 arm) to walk outdoors
- **3**: Usually uses bilateral support to walk outdoors
- **4**: Usually uses wheelchair to travel outdoors. Able to stand and walk a few feet
- **5**: Restricted to wheelchair, unable to stand and walk a few steps with help
### I-RODS: Inflammatory (Neuropathy) Rasch-built Overall Disability Scale

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

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

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

<table>
<thead>
<tr>
<th>Acute GBS</th>
<th>Subacute</th>
<th>CIDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4 weeks</td>
<td>4 - 8 weeks</td>
<td>&gt; 8 weeks</td>
</tr>
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</table>

What factors account for the differences in temporal pattern?
1980- CIDP Is A Disease

CIDP

Myeloma Neuropathy
• 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 (e.g. Plexus)

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

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

• Clinical diagnostic criteria
  o Typical: > 2 months, relapsing or progressive, symmetric proximal/distal, reduced DTRs
  o 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

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.......
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 criteria-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

• Contactin Ab causes severe CIDP
  o 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

CIDP

IV/SC Immunoglobulin
(e.g., Gamunex, Hizentra)
- Very effective
- Side effects and complications (e.g., severe headaches, thromboembolic events, hemolysis, hematologic changes).
- Long IV and SC infusions due to the large volumes.

Corticosteroids
(e.g., methylprednisolone)
- Inexpensive
- Effective
- Chronic use is limited by adverse events
  - Weight gain
  - Cushingoid appearance
  - Cataracts
  - Osteoporosis
  - Hypertension and diabetes

Plasma Exchange
- Effective for the short-term treatment
- Invasive procedure
- Susceptible to clotting and infection
- Only available at specialized centers
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
  o INCAT; R-ODS; Grip; TUG;
  o Manual Muscle Testing with MRC noting the muscles that are mildly weak

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

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

• Aggressive disease with significant functional deficits requires early response
  o IVIg is more likely than pulse steroids to provide early improvement
  o PLEX works at least as rapidly as IVIg

• Young patients not agreeable to cushingoid appearance
  o Pulse steroids rather than daily
  o IVIg induction
  o IV or SClg maintenance

• Older patients have risks of osteoporosis, fractures, and diabetes, hypertension
  o IVIg may be more safe than steroids
  o 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
  o Still lacking pathophysiologic insights

• Treatments providing long-term remission are within reach

• Treatments that can control disease with minimal risk and inconvenience
  o 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

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

1. Antigen presentation by APCs
2. Activation of B-cells and T-cells, autoantibody release
3. Blood-nerve barrier breakdown, target engagement by autoantibodies
4. Further enforcement of inflammation
5. Tissue damage and demyelination

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

2. Activate complement
   - Complement deposition
   - C5b-9MAC

3. Recruit macrophages
   - Macrophage infiltration
   - Fc receptor

From: Mathey et al, J Neurol Neurosurg Psychiatry. 2015;86(9):973-85
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
Increasing Selectivity for IgG Reductions Maintains Therapeutic Efficacy

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

Clinical evidence for the role of pathogenic autoantibodies in CIDP

- Oaklander et al (2017), Cochrane Database Syst Rev
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

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Plasma exchange</th>
<th>Sham exchange</th>
<th>Significance †</th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Clinical measure:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological disability score Clinical grade</td>
<td>73.3 ± 5.3</td>
<td>35.3 ± 4.5</td>
<td>69.4 ± 6.4</td>
</tr>
<tr>
<td>Grip strength (kg)</td>
<td>4.6 ± 0.4</td>
<td>3.0 ± 0.4</td>
<td>4.3 ± 0.4</td>
</tr>
<tr>
<td>Electrophysiological measure:</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Σ proximal CMAP (mV)</td>
<td>7.3 ± 1.2</td>
<td>11.0 ± 1.9</td>
<td>7.1 ± 1.9</td>
</tr>
<tr>
<td>Σ distal CMAP (mV)</td>
<td>15.0 ± 2.0</td>
<td>17.3 ± 2.6</td>
<td>12.7 ± 2.3</td>
</tr>
<tr>
<td>Σ motor conduction velocity (m s⁻¹)</td>
<td>91.3 ± 11.9</td>
<td>104.5 ± 11.2</td>
<td>86.7 ± 9.4</td>
</tr>
<tr>
<td>Σ distal motor latency (ms)</td>
<td>34.7 ± 5.5</td>
<td>29.1 ± 2.9</td>
<td>35.3 ± 4.7</td>
</tr>
</tbody>
</table>

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

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

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Responders N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLEX</td>
<td>4/9 (44.4)</td>
</tr>
<tr>
<td>IA</td>
<td>6/9 (66.7)</td>
</tr>
</tbody>
</table>

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.

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

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

CIDP patients can benefit from repeated IgG removal using IA

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 (unknown antigens)

Myelin Sheath (produced by Schwann cells)

Neuron

Axon

Myelin Sheath

Anti-myelinated proteins

Anti-paranodal proteins

Paranodal proteins: eg. NF155, contactin-1

Nodal proteins: eg. NF186, gliomedin

Autoantibodies

Axon

Myelin Sheath

Anti-myelinated proteins

Anti-paranodal proteins

Paranodal proteins: eg. NF155, contactin-1

Nodal proteins: eg. NF186, gliomedin

Autoantibodies
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

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

Manso et al (2016), Brain 139: 1700–1712
Ng et al (2012), Neurology 79: 2241-2248
Autoantibody Levels to Paranodal Junction Correlate with Disease Severity

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

**Mouse teased sciatic nerves**

- CIDP serum IgG
- Nodal marker

**Table 1.** Percentage of sera that bound axonal compartments.

<table>
<thead>
<tr>
<th>Percentage of sera that stained</th>
<th>NC</th>
<th>CIDP</th>
<th>OND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Node</td>
<td>0</td>
<td>20 (12)†</td>
<td>3.8 (3)</td>
</tr>
<tr>
<td>Paralod</td>
<td>0</td>
<td>18 (6)†</td>
<td>0</td>
</tr>
<tr>
<td>Any compartments</td>
<td>0</td>
<td>30</td>
<td>3.8</td>
</tr>
</tbody>
</table>

OND: other neurological disorders

**Cultured Schwann cells**

- Table 1 Anti-Schwann cell IgG immunofluorescence

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

**33% of CIDP patients have IgGs binding to myelinated nerves**

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

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

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

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

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

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

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

**Identify patients with active CIDP**

- Confirmation of diagnosis by independent committee

**Screening**

- ≤4 weeks

**Run-in period**

- Worsening of disease within 12 weeks after drug withdrawal (INCAT, I-RODS, grip strength)
- Newly diagnosed/treatment naïve skip Run-in period

- ≤13 weeks

**Stage A**

- Confirm IgG autoantibody involvement

**Stage B** (stage A responders only)

- Document efficacy & safety efgartigimod vs placebo

- 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

- Open label Placebo-controlled

- Placebo weekly SC

- Efgartigimod weekly SC

- Up to 12 weeks, until clinical improvement (ECI)

- Up to 48 weeks
### GO/NO Decision During ADHERE Study

**Screening**
- Confirmation of diagnosis by independent committee

**Run-in period**
- Worsening of disease within 12 weeks after drug withdrawal (INCAT, I-RODS, grip strength)
- Newly diagnosed/treatment naïve skip Run-in period

<table>
<thead>
<tr>
<th>Stage A</th>
<th>Stage B (stage A responders only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open label</td>
<td>Placebo-controlled</td>
</tr>
</tbody>
</table>

#### Treatment period

<table>
<thead>
<tr>
<th>Period</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4 weeks</td>
<td>Screening</td>
</tr>
<tr>
<td>≤13 weeks</td>
<td>Run-in period</td>
</tr>
<tr>
<td>Up to 12 weeks, until clinical improvement (ECI)</td>
<td>Stage A (Efgartigimod weekly SC)</td>
</tr>
<tr>
<td>Up to 48 weeks</td>
<td>Stage B (Efgartigimod weekly SC)</td>
</tr>
</tbody>
</table>

**Efficacy analysis**
- 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 Go**
- N=30
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

Effective FcRn blockade requires >2mL volume regardless of modality

How do you solve for this?

ENHANZE® enables single subcutaneous injection of >2mL
ENHANZE® Drug Delivery Technology Offers Optionality to Patients

Drug material from IV infusion...

• Hospital/clinic or infusion service
• Administered by HCP
• Weight-based infusion
• ≤60 minutes

…into single subcutaneous injection

• At-home convenience
• Self-administered
• Flat dose single injection
• As fast as 1 minute

No premedication needed
Commercially-Validated ENHANZE® Drug Delivery Technology

4 Globally-Approved or Late-Stage Development and 9 Partnerships in Place

- **Co-formulated**
  - Efgartigimod 5.5mL
  - Darzalex®

- **Co-administered**
  - HyQvia
    - Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase
  - Rituxan HYCELA
    - Rituximab/hyaluronidase human

- **Injection Times**
  - Shorter injection time: 5mL
  - 2-5 minute injection: 15mL
  - Longer administration: 300mL+
ENHANZE® permits rapid administration of larger volumes SC and can reduce frequency of administration.

SC Injection Pressures

- Significantly higher injection pressure without ENHANZE®
- Reduced injection pressure with ENHANZE®
Phase 1 HV Study Trial Evaluated Multiple Dose Levels of ENHANZE® Efgartigimod SC Formulation

- **Treatment A**: Single SC dose @750 mg, N = 8
- **Treatment B**: Single SC dose @1250 mg, N = 8
- **Treatment C**: Single SC dose @1750 mg, N = 8
- **Treatment D**: Single SC dose @10 mg/kg, N = 8

**SCREENING** 21 days

18-70 yrs

(BW range 50-100 kg)

Interim analysis
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

- Potential for home and self-administration
- Fine needle size (low viscosity)
- Patient comfort
- Injected in under 1 minute (5.5mL volume)
- Simple push (minimal effort)
Advancing ENHANZE® Efgartigimod SC into Development Pipeline

IV Efgartigimod

ENHANZE® SC Efgartigimod

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
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), 24%

Primary Immune Deficiencies (PID), 23%

Chronic ITP, 7%

Chronic Lymphocytic Leukemia (CLL), 4%

Multifocal Motor Neuropathy (MMN), 4%

Diabetic Neuropathy, 2%

Guillan Barre Syndrome, 2%

Acute Idiopathic Thrombocytopenic Purpura (ITP), 2%

SLE (lupus), 2%

Myasthenia Gravis, 1-2%

Alzheimer’s, 2%

All others, 26%

CIDP is a ~$2.6B market opportunity
Expected to grow double digit per year

Total IVIg market $11.1 Bn; 9% CAGR
Thank You