Welcome

Ron Cohen, MD
President and CEO
Forward Looking Statements

This presentation includes forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements, other than statements of historical facts, regarding management’s expectations, beliefs, goals, plans or prospects should be considered forward-looking. These statements are subject to risks and uncertainties that could cause actual results to differ materially, including our ability to successfully market and sell Ampyra in the U.S.; third party payers (including governmental agencies) may not reimburse for the use of Ampyra or our other products at acceptable rates or at all and may impose restrictive prior authorization requirements that limit or block prescriptions; the risk of unfavorable results from future studies of Ampyra or from our other research and development programs, including Diazepam Nasal Spray or any other acquired or in-licensed programs; we may not be able to complete development of, obtain regulatory approval for, or successfully market Diazepam Nasal Spray or other products under development; the occurrence of adverse safety events with our products; delays in obtaining or failure to obtain regulatory approval of or to successfully market Fampyra outside of the U.S. and our dependence on our collaboration partner Biogen Idec in connection therewith; competition, including the impact of generic competition on Zanaflex Capsules revenues; failure to protect our intellectual property, to defend against the intellectual property claims of others or to obtain third party intellectual property licenses needed for the commercialization of our products; failure to comply with regulatory requirements could result in adverse action by regulatory agencies; and the ability to obtain additional financing to support our operations. These and other risks are described in greater detail in Acorda Therapeutics’ filings with the Securities & Exchange Commission. Acorda may not actually achieve the goals or plans described in its forward-looking statements, and investors should not place undue reliance on these statements. Forward-looking statements made in this presentation are made only as of the date hereof, and Acorda disclaims any intent or obligation to update any forward-looking statements as a result of developments occurring after the date of this presentation.
Introduction of Acorda Management

Andrew Blight, PhD
Chief Scientific Officer

Enrique Carrazana, MD
Chief Medical Officer

Anthony Caggiano, MD, PhD
VP, Research & Development

Ron Cohen, MD
President & CEO
<table>
<thead>
<tr>
<th>Guest Speakers</th>
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<tbody>
<tr>
<td><strong>Seth Finklestein, MD</strong></td>
</tr>
<tr>
<td>Chairman, Founder and Chief Executive Officer, Biotrofix, Inc.</td>
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<tr>
<td><strong>Rajiv R. Ratan, MD, PhD</strong></td>
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<tr>
<td>Executive Director, The Burke Medical Research Institute</td>
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<tr>
<td><strong>Daniel J. Lenihan, MD</strong></td>
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<tr>
<td>Professor of Medicine, Vanderbilt University Medical Center</td>
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<tr>
<td><strong>Jacqueline French, MD</strong></td>
</tr>
<tr>
<td>Professor of Neurology, New York University</td>
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<tr>
<td><strong>Moses Rodriguez, MD</strong></td>
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<tr>
<td>Professor of Neurology and Immunology Mayo Clinic College of Medicine</td>
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</tbody>
</table>
Acorda’s Strategy for Growth

1. Maximize AMPYRA franchise
2. Advance pipeline to market
3. Acquire additional assets that leverage existing commercial and development expertise
# Acorda’s 2011 Pipeline

<table>
<thead>
<tr>
<th>THERAPY</th>
<th>R&amp;D</th>
<th>PRE CLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3/4</th>
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<tbody>
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<td>AMPYRA®</td>
<td>Walking in MS</td>
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<td>ZANAFLEX®</td>
<td>Spasticity</td>
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<td>GGF2</td>
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<td>Stroke/SCI/PN</td>
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<td>rHlgM22</td>
<td>MS</td>
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<td>SCI</td>
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## Acorda’s Pipeline in 2013

<table>
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<th>R&amp;D</th>
<th>PRE CLINICAL</th>
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<tr>
<td>DALFAMPRIODINE-QD</td>
<td>Post-Stroke Deficits</td>
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<tr>
<td>ZANAFLEX®</td>
<td>Spasticity</td>
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<tr>
<td>QUTENZA®</td>
<td>Post-Shingles Nerve Pain</td>
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<tr>
<td>NP-1998</td>
<td>Neuropathic Pain</td>
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<tr>
<td>DIAZEPAM NASAL SPRAY</td>
<td>Cluster Seizures</td>
<td></td>
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<tr>
<td>GGF2</td>
<td>Heart Failure</td>
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<td>AC105</td>
<td>SCI</td>
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<td>CHONDROITINASE</td>
<td>SCI</td>
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</tbody>
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Dalfampridine in Post-Stroke Walking Deficits

Andrew Blight, PhD
Chief Scientific Officer
Stroke Disease State and Preclinical Overview

Seth Finklestein, MD
Stroke Overview

• ~7 million people in US have had a stroke¹
  – ~Half have mobility issues²
  – ~800,000 new cases reported annually³

• Stroke is one of the leading causes of long-term disability
  – On average, someone in the United States has a stroke every 40 seconds
  – Someone in the U.S. dies of stroke every 4 minutes

• Stroke is the third cause of death in the U.S.

¹ AHA Heart and Stroke Update 2011; ² National Institute of Neurological Disorders and Stroke; ³ AHA 2011
Stroke Definition

- Blood flow to a part of the brain is interrupted, depriving it of blood, oxygen, and nutrients
- Brain cells can die, potentially causing permanent damage, disability, and death
Ischemic Stroke

- Ischemic stroke – by far the most common kind of stroke; accounts for ~88 percent of all strokes\(^1\)
- Ischemic strokes happen when blood clots block the blood vessels to the brain
- Many people with ischemic strokes are older (60 or more years old)
- Risk of stroke increases with age

\(^1\) Adapted from Albers GW, et al. Chest 2004; 126:483S512S; Image: The Internet Stroke Center
Myelin Damage in Stroke

• Oligodendrocytes in both white and gray matter are highly sensitive to ischemic stress in animal models\(^1\)
• In a study of ischemic stroke patients (n=42) enrolled in neuroprotective trials\(^2\)
  – ~ 50% of the infarct volume was white matter
  – ~ 95% of the patients had at least some involvement of white matter tracts
• White matter involvement may be associated with poorer functional outcomes after stroke\(^3\)

Preclinical Study in Rat MCAO Model

- Dalfampridine evaluated in a permanent middle cerebral artery occlusion (pMCAO) rat model of chronic stroke
- Dosing started at 4 weeks after stroke
- 3 groups (n=15) treated orally over 3 separate 3 day periods
- 10 day washout between treatment periods
- Each group with different order of dosing across these periods:
  - Group 1: High dose, Low dose, Vehicle control
  - Group 2: Low dose, Vehicle control, High dose
  - Group 3: Vehicle control, High dose, Low dose
- Behavioral assessment of sensorimotor limb function
- Statistical analysis using mixed-model ANOVA
Dalfampridine Improved Function in a Preclinical Model of Post Stroke Deficits

Iaci, et al. Stroke 2013
Confirmatory Preclinical Study at 8 Weeks Post-Stroke

Dose escalation study design

Iaci, et al. Stroke 2013
Stroke Overview

• Stroke costs the United States an estimated $38.6 billion each year\(^1\)
  – This total includes the cost of health care services, medications, and missed days of work

• No drug therapy indicated to address functional impairment in people with post-stroke walking deficits

Stroke Disability

- Growing public health problem across the globe
- Current estimates are that by 2050, the U.S. government will be spending $350 billion a year on stroke care
- We cannot wait another 20 years to act on this daunting prediction
No Definitive Treatments for Gait After Stroke

- Robotics
- Non invasive brain stimulation
- Fluoxetine (acute)
- Mesenchymal stem cells
- Drugs that enhance nerve regeneration (Rho A inhibitors)
- Drugs that increase neurotransmitter tone (Amantadine)
- Diet (ketogenic diet)
Issues Post-Stroke

- Daily living skills (walking)
- Dressing and grooming
- Diet, nutrition and eating difficulties
- Skin care problems
- Pain
- Sexuality/Intimacy

- Behavior
- Depression & Anger
- Emotional Liability
- One-sided Neglect
- Memory Loss
- Communication Problems
Traditional Aim of Rehabilitation

- Impairment: Stroke hemiparesis
- Disability: Impaired walking
  - Occupational therapy
  - Physical therapy
  - Assistive devices
- Handicap: Unable to work or socialize
Restoring or improving ability to walk is a major goal of post-stroke rehabilitation¹

Walking speed is regarded as significant, sensitive and reliable marker of deficit severity and functional community walking ability¹,²

<table>
<thead>
<tr>
<th>Mean Walking Speed per 10 Meter Walk Test (m/sec)</th>
<th>Mean Walking Speed (ft/sec)</th>
<th>Functional Ambulation Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.16-0.25</td>
<td>0.52-0.82</td>
<td>Restricted indoor ambulation</td>
</tr>
<tr>
<td>0.26-0.42</td>
<td>0.85-1.38</td>
<td>Unrestricted indoor ambulation</td>
</tr>
<tr>
<td>0.43-0.79</td>
<td>1.41-2.59</td>
<td>Restricted community ambulation</td>
</tr>
<tr>
<td>0.80-1.20</td>
<td>2.62-3.94</td>
<td>Slow unrestricted community ambulation</td>
</tr>
</tbody>
</table>

Andrew Blight
Chief Scientific Officer

Overview of Post Stroke Proof-of-Concept Study
Proof of Concept Study in Post-Stroke

- Double-blind, randomized, crossover design
- 83 people with ischemic stroke at least 6 months prior, currently with stable neurological deficits
  - Participants received both dalfampridine-ER 10 mg and placebo for 14 days twice daily, with one week washout
- Proof-of-concept data on:
  - Safety and tolerability
  - Primary efficacy focus on walking (Timed 25-Foot Walk)
    - Other efficacy measures included upper and lower extremity sensorimotor function, global measures
Study Design
# Patient Disposition, Demographics, and Stroke History

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sequence A (PBO→D-ER)</th>
<th>Sequence B (D-ER→PBO)</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomized, n</td>
<td>55</td>
<td>28</td>
<td>83</td>
</tr>
<tr>
<td>Safety population, n (%)</td>
<td>55 (100)</td>
<td>28 (100)</td>
<td>83 (100)</td>
</tr>
<tr>
<td>Full-analysis population, n (%)</td>
<td>52 (94.5)</td>
<td>26 (92.9)</td>
<td>78 (94.0)</td>
</tr>
<tr>
<td>Patients completing study, n (%)</td>
<td>45 (81.8)</td>
<td>25 (89.3)</td>
<td>70 (84.3)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18 (32.7)</td>
<td>10 (35.7)</td>
<td>28 (33.7)</td>
</tr>
<tr>
<td>Male</td>
<td>37 (67.3)</td>
<td>18 (64.3)</td>
<td>65 (66.3)</td>
</tr>
<tr>
<td>Age, years</td>
<td>Mean (SE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>57.5 (1.31)</td>
<td>63.5 (1.68)</td>
<td>59.5 (1.08)</td>
</tr>
<tr>
<td>No. of ischemic strokes, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>45 (81.8)</td>
<td>20 (71.4)</td>
<td>65 (78.3)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>10 (18.2)</td>
<td>8 (28.6)</td>
<td>18 (21.7)</td>
</tr>
<tr>
<td>Months since last stroke, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>53.1 (9.2)</td>
<td>43.1 (6.4)</td>
<td>49.7 (6.5)</td>
</tr>
<tr>
<td>(min, max)</td>
<td>(5.0, 417.5)</td>
<td>(7.0, 130.0)</td>
<td>(5.0, 417.5)</td>
</tr>
<tr>
<td>Location of last stroke, a n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>30 (54.5)</td>
<td>14 (50.0)</td>
<td>44 (53.0)</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>9 (16.4)</td>
<td>7 (25.0)</td>
<td>16 (19.3)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (29.1)</td>
<td>7 (25.0)</td>
<td>23 (27.7)</td>
</tr>
</tbody>
</table>

a Two subjects experienced stroke in more than 1 location and were counted twice.

D-ER, dalfampridine extended release; PBO, placebo; SE, standard error.
# Reasons for Early Termination (n=13)

<table>
<thead>
<tr>
<th>Reason for Early Termination</th>
<th>No. of Patients</th>
<th>Investigational Drug</th>
<th>Treatment Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse event</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td>2</td>
<td>D-ER(^a)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>PBO</td>
<td>A</td>
</tr>
<tr>
<td>Nausea and insomnia</td>
<td>1</td>
<td>D-ER</td>
<td>B</td>
</tr>
<tr>
<td>General malaise</td>
<td>1</td>
<td>D-ER</td>
<td>A</td>
</tr>
<tr>
<td>Left lower-extremity weakness</td>
<td>1</td>
<td>D-ER</td>
<td>B</td>
</tr>
<tr>
<td><strong>Noncompliance</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>With investigational drug</td>
<td>3</td>
<td>PBO</td>
<td>A</td>
</tr>
<tr>
<td>With the protocol</td>
<td>1</td>
<td>D-ER</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>PBO</td>
<td>A</td>
</tr>
<tr>
<td><strong>Withdrew consent</strong></td>
<td>1</td>
<td>PBO</td>
<td>B</td>
</tr>
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</table>

\(^a\) Secondary to an intentional overdose in 1 patient.

D-ER, dalfampridine extended release; PBO, placebo.
# Most Common Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>Preferred Term, n (%)</th>
<th>PBO (n=81)</th>
<th>D-ER (n=77)</th>
<th>All Patients (n=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>2 (2.5)</td>
<td>8 (10.4)</td>
<td>10 (12.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (6.2)</td>
<td>3 (3.9)</td>
<td>8 (9.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (3.7)</td>
<td>4 (5.2)</td>
<td>7 (8.4)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2 (2.5)</td>
<td>4 (5.2)</td>
<td>6 (7.2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (3.7)</td>
<td>2 (2.6)</td>
<td>5 (6.0)</td>
</tr>
</tbody>
</table>

*≥5% for either treatment or in the total population.

D-ER, dalfampridine extended release; PBO, placebo.
### Serious Adverse Events

<table>
<thead>
<tr>
<th>Preferred Term, n (%)</th>
<th>PBO (n=81)</th>
<th>D-ER (n=77)</th>
<th>All Patients (n=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convulsion</td>
<td>1 (1.2)</td>
<td>2 (2.6)</td>
<td>3 (3.6)</td>
</tr>
<tr>
<td>Microcytic anemia</td>
<td>0</td>
<td>1 (1.3)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (1.2)</td>
<td>0</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dehydration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intentional overdose</td>
<td>0</td>
<td>1 (1.3)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Suicide attempt</td>
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</tbody>
</table>

D-ER, dalfampridine extended release; PBO, placebo.
Treatment Effect of D-ER on Overall Walking Speed (Full-Crossover Model)

n=78, P=0.027
Mean Change from Baseline in Walking Speed (By Sequence and Period; Full-Analysis Population)

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Period 1</th>
<th>Period 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence A</td>
<td>Mean 0.24, SE 0.04</td>
<td>Mean 0.17, SE 0.06</td>
</tr>
<tr>
<td>Sequence B</td>
<td>Mean 0.17, SE 0.06</td>
<td>Mean 0.09, SE 0.04</td>
</tr>
</tbody>
</table>

Period 1: P = 0.058
Period 2: P = 0.195
Percentages of Patients Reaching Threshold Change from Baseline in Walking Speed in Period 1
Percentages of Patients Reaching Threshold Change from Baseline in Walking Speed in Period 2

Period 2

Patients (%)

Increase in Walking Speed from Baseline

≥0%  ≥10%  ≥20%  ≥30%  ≥40%  ≥50%

PBO (n=26)
D-ER (n=49)
Conclusions from POC Study

• D-ER improved walking speed in a subset of patients with chronic sensorimotor deficits, similar to effects previously shown in MS
• D-ER was generally well tolerated in patients with chronic sensorimotor deficits after an ischemic stroke
• Safety profile was consistent with that seen in previous studies as well as in post marketing safety assessments of people with MS
Post-Stroke Deficits - Next Steps

- Meeting with FDA by YE2013
- QD Formulation
  - Single-dose PK studies completed
  - Multi-dose PK verification study to be initiated this year
  - May provide improved convenience, compliance and tolerability
  - Additional IP
- Phase 2b/3 study expected to begin in Q2 2014
  - Parallel group study comparing 2 doses to placebo
  - Possible interim analysis
  - Walking as a primary endpoint
Diazepam Nasal Spray Opportunity

Enrique Carrazana, MD, Chief Medical Officer
Diazepam Nasal Spray Opportunity

- ~2.3 million Americans have active epilepsy*
- ~175,000 people with cluster seizures
  - Orphan drug indication
- Significant underserved market
  - Only approved treatment is rectal gel
  - Limited uptake in adults
  - Many patients default to emergency room
- Nasal spray offers patients and caregivers a convenient option for cluster seizures
- Leverages existing commercial and development organizations

*Centers for Disease Control 2010
Seizure Medications Over the Last 150 Years

In the modern era: one third of patients are still refractory

Diastat Administration

1. Put person on their side where they can’t fall.
2. Get medicine.
3. Get syringe. Note: Seal Pin is attached to the cap.
4. Push up with thumb and pull to remove cap from syringe. Be sure Seal Pin is removed with the cap.
5. Lubricate rectal tip with lubricating jelly.
6. Turn person on side facing you.
7. Bend upper leg forward to expose rectum.
8. Separate buttocks to expose rectum.
9. Gently insert syringe tip into rectum. Note: Rim should be snug against rectal opening.
10. Slowly count to 3 while gently pushing plunger in until it stops.
11. Slowly count to 3 before removing syringe from rectum.
12. Slowly count to 3 while holding buttocks together to prevent leakage.

Sources: Diastat product insert
Diazepam Nasal Spray Overview

- NDA filed
- 505(b)(2) NDA based on Diastat® (diazepam rectal gel)
  - Diazepam nasal spray references safety and efficacy data from Diastat and includes safety associated with nasal administration
  - Diastat indicated for increased bouts of seizure activity
- Orphan drug designation
  - 7 years exclusivity
- Potential launch in 2014
Epilepsy Disease State

Jacqueline French, M.D.
NYU Comprehensive Epilepsy Center
International League Against Epilepsy (ILAE) Definitions

Epileptic Seizure
- Transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain

Epilepsy
- Disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure
Incidence of Epilepsy

- Conservatively, ~50 million people worldwide have epilepsy\(^1\)
- Annual incidence ranges from 20-70 cases per 100,000
- Overall, 5% of persons report a seizure at some time in their lives (excluding febrile seizures)
  - Incidence rates are highest in childhood
  - Plateau from 15-65 years of age; rise among the elderly
- About 30% of patients with seizures have an identifiable neurologic or systemic disorder; remainder have either idiopathic or cryptogenic epilepsy
- The diagnosis is based on the description of the seizures and the clinical context in which they occur, often supplemented by the results of electroencephalography

Consequences of Uncontrolled Seizures

- Shortened life span
- Bodily injury, hospitalization
  - Status epilepticus
- Neuropsychological and psychiatric impairment
  - Depression
  - Reduced quality of life
- Social disability
  - Reduced marriage rates
  - Reduced employment
## Outcome With Initial Drug Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Seizure Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>First drug monotherapy</td>
<td>47%</td>
</tr>
<tr>
<td>Second drug monotherapy</td>
<td>13%</td>
</tr>
<tr>
<td>Third drug monotherapy</td>
<td>1%</td>
</tr>
<tr>
<td>Duotherapy</td>
<td>3%</td>
</tr>
<tr>
<td>Refractory epilepsy</td>
<td>36%</td>
</tr>
</tbody>
</table>

Preventive (antiepileptic medications)
- Standard for nearly all patients
- Not effective for an “acute” seizure

Abortive or rescue medications
- Seizures in clusters
- Prolonged seizures
- Status epilepticus
Seizure Clusters
(Acute Repetitive Seizures)

• Seizure pattern in which several seizures occur within a 24-hour period followed by a longer seizure-free interval (weeks-months)
• Easily recognizable pattern
• Initial seizure predicts subsequent seizures
Time Sequence of Seizures

EACH VERTICAL BAR IS ONE SEIZURE

Menstruation

DRUG STUDY SEIZURE DIARY

After Fisher, R
Impact of Clusters

• Seizure clusters are very disruptive to patients
• May produce “dysfunctional days”
• May lead to ER visits
• Increase likelihood of status epilepticus
Treating Seizure Clusters

• Seizure clustering is a common component of treatment resistant epilepsy
• If a patient knows from prior experience that more seizures are expected, why not try to prevent them?
Ideal Drug Characteristics for Emergency Treatment of Seizures

- Effective against all seizure types
- Will not exacerbate any seizure type
- Potent
- Easily administered (nasal, rectal, IM, IV)
- Rapid onset of action
- Intermediate duration of action
- No alteration of consciousness
- No adverse side effects
Benefits of Diazepam

- Works for all types of seizures
- Works rapidly
- Chronic use may induce tolerance
- Hit-and-run
- Proven safe and effective
Advantages of Nasal Drug Delivery

• Easy access with/without patient cooperation
• Rapid and extensive absorption through the nasal mucosa
• Convenient and easy administration
• Needle-less
Diazepam Nasal Spray Summary

- ~2.3 million Americans have active epilepsy*
- ~175,000 people with cluster seizures
- Significant underserved market
- Nasal spray offers patients and caregivers a convenient option for cluster seizures
- Leverages existing commercial and development organizations
- Launch readiness ongoing

*Centers for Disease Control 2010
Qutenza® & NP-1998 Opportunities in Neuropathic Pain

Enrique Carrazana, MD
Neuropathic Pain Assets

• Qutenza® (capsaicin) 8% patch
  – FDA-approved dermal patch therapy indicated for the management of postherpetic neuralgia (PHN), also known as shingles nerve pain
  – Supporting product using Acorda’s existing commercial and medical infrastructure

• NP-1998
  – Phase 3 ready, topical solution containing 20% prescription strength capsaicin targeting neuropathic pain
  – Astellas currently studying Qutenza in painful diabetic neuropathy (PDN) which will inform next steps with NP-1998
Active Ingredient: Capsaicin

- Capsaicin is a highly selective and potent agonist for the transient receptor potential vanilloid 1 receptor (TRPV1)
  - TRPV1 is preferentially expressed on small-diameter sensory neurons
- Treatment with therapeutic concentration of capsaicin:
  - Long-lasting desensitization of terminal branches of cutaneous sensory nerves expressing TRPV1
  - Reduced sensitivity to pain and other stimuli
Neuropathic Pain Overview

- Neuropathic pain (NP) is pain that arises from damage to the central and/or peripheral nervous systems.
- Patient populations are often subdivided on the basis of the underlying etiology of the disease:
  - Post-herpetic neuralgia (PHN)
  - Painful diabetic neuropathy (PDN)
  - Neuropathic back pain
  - HIV/AIDS-related NP
  - Post-trauma/postsurgical NP
  - Neuropathic cancer pain
## Prevalence of NP Populations

### U.S. Prevalent Cases for Select NP Populations, 2011-2021

<table>
<thead>
<tr>
<th>Condition</th>
<th>2011</th>
<th>2016</th>
<th>2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful diabetic neuropathy</td>
<td>3.2M</td>
<td>3.8M</td>
<td>4.3M</td>
</tr>
<tr>
<td>Post-herpetic neuralgia</td>
<td>172,940</td>
<td>153,360</td>
<td>149,900</td>
</tr>
<tr>
<td>HIV/AIDS-related NP</td>
<td>566,530</td>
<td>615,500</td>
<td>657,490</td>
</tr>
</tbody>
</table>

1 Decision Resources July 2013
Qutenza Product Summary

- Indicated for the management of pain associated with PHN
- Approved in 2010; reported net sales of $2.6 million in 2011
- Leverages Acorda’s existing commercial and medical infrastructure
- Orphan exclusivity to November 2016
Qutenza Benefits

- 12 weeks’ duration of action with a single dose
- Efficacy similar to systemic drugs
  - Avoids systemic side effects commonly seen with centrally acting treatments
  - Can be used in together with systemic drugs
- Not a controlled substance (in contrast to opioids)
- Leverages Acorda’s existing commercial and medical infrastructure
Qutenza Limitations

- PHN is a small indication
- FDA labeling in the US requires Qutenza to be administered by a physician
- Buy and bill for Medicare patients creates perceived financial risks
- Requires pre-treatment of the painful area with a topical anesthetic
- Total treatment time typically 2.5 hours including the 60 minutes during which Qutenza patch is on patient
  - Long treatment time raises logistical issues in physicians’ practices
NP-1998 Overview

- Liquid formulation containing 20% capsaicin
  - Applied to the patient using an applicator
- 15 minute total procedure time
- Single 5 minute application shown to provide 3 months of pain relief
- U.S. patent extends to 2027
Pharmacodynamic Effect of a 5-minute NP-1998 Compared to 60-minute Qutenza: C202

Epidermal Nerve Fiber Immunostaining (PGP 9.5)

Percent of Control

Qutenza (60-min)  NGX-1998 (25-min)  NP-1998 (15-min)  NP-1998 (5-min)
Next Steps

- Awaiting results of Astellas study of Qutenza in PDN
  - Potential to address large markets
  - 3.2 million Americans with PDN
- Results will determine next development steps for NP-1998
Heart Failure and GGF2 Development Program

Anthony Caggiano, MD, PhD
VP, Research & Development
GGF2 (USAN: cimaglermin alfa)

- Natural growth factor related to EGF
- Therapeutic targets for treatment of cardiac and neurological repair
- Fast Track designation from FDA
- Phase 1 study in Chronic Heart Failure completed
  - Tolerability of a single infusion over a range of doses
  - GGF2 improved function as measured by ejection fraction
- Second Phase 1 study currently recruiting in Chronic Heart Failure
  - Further define safety and efficacy profile
  - Explore potential drug interactions
Heart Failure Overview

Daniel J. Lenihan, MD
Vanderbilt University
Clinical Manifestations of Heart Failure

Clinical Manifestations:
- Asymptomatic LVD
- Congestive state
- Low-output state
- Cardiogenic shock
- Combinations
Epidemiology of Heart Failure

Heart Failure Patients in U.S.
Millions of HF cases, more than 65 years of age

1993: 3.5
2000: 4.9
2033: 7.0

Neurohormonal Factors

Factors elevated in patients with heart failure

- Norepinephrine
- Angiotensin II
- Aldosterone
- Endothelin

- Arginine vasopressin (ADH)
- Tumor necrosis factor-alpha
- Natriuretic peptides (BNP, ANP)
- IL-6, and other inflammatory markers
Established Therapies

Drugs with a mortality benefit in heart failure patients

- Angiotensin converting enzyme inhibitors (ACE-I)
- Beta-blockers
- Spironolactone, Eplerenone
- Angiotensin Receptor Blocker (Candesartan)
- Isordil/Hydralazine
Effect of Various Treatments on Mortality in Heart Failure

\[ \text{NNT}_x \text{ years} = \frac{100}{(\% \text{Mortality in Control Group} - \% \text{Mortality in Treatment Group})} \]

- **CRT**
  - COMPANION: 25
  - MUSTT: 14
  - MADIT: 3
  - MADIT II: 4
  - AVID: 11
  - COPERNICUS: 9
- **ICD**
  - SAVE: 14
  - CIBIS II: 20
  - MERIT HF: 25
  - CAPRICORN: 29
  - Amdocor: 29
  - HOPE: 37

Years of tested treatment:
- 1 Yr
- 5 Yr
- 2.4 Yr
- 3 Yr
- 3 Yr
- 0.8 Yr
- 3.5 Yr
- 1 Yr
- 1 Yr
- 1.5 Yr
- 2 Yr
- 4 Yr

Abraham, Circ 2004:
Neuregulins in Cardiac Repair and Stress Response

Endothelial Cell

NRG Release:
- Ischemia
- Stress
- Exercise

Cardiac Myocyte

Cardiac Repair
Increased Cell Survival

Wells, Q; et al, Prog in CV Diseases 2010
Completed Phase 1a Trial: Objectives

Primary
• Evaluate the safety and tolerability of single, escalating doses of GGF2

Secondary
• Evaluate cardiac function after single dose of GGF2
| Study Design          | - Phase-1, Single Ascending Dose  
|                      | - Double-blind, placebo-controlled |
| Key Inclusion Criteria | - LVEF 10-40% screening  
|                       | - NYHA Class II-III  
|                       | - Cancer-free  
|                       | - ICD in place  
| Methods               | - Single IV infusion  
|                       | - 6 patients per cohort (4 GGF2:2 placebo)  
|                       | - Escalating dose (0.007-1.512 mg/kg)  
| Evaluation            | Safety Clinical  
|                       | - ECG, Holter monitor  
|                       | - Echocardiography (EF)  
|                       | - BNP, Troponin  

Primary measurements (2D):
- Ejection Fraction
- End-Diastolic Volume
- End-Systolic Volume
# Patient Profile

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Placebo</th>
<th>GGF2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N = 40</strong></td>
<td></td>
<td><strong>N = 13</strong></td>
<td><strong>N = 27</strong></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>57.4 (9.8)</td>
<td>54.7 (13.2)</td>
<td>58.6 (7.7)</td>
</tr>
<tr>
<td><strong>Male/Female</strong></td>
<td>33 (83%) / 7 (17%)</td>
<td>12(92%) / 1(8%)</td>
<td>21(78%) / 6(22%)</td>
</tr>
<tr>
<td><strong>Caucasian</strong></td>
<td>36 (90%)</td>
<td>12(92%)</td>
<td>24 (89%)</td>
</tr>
<tr>
<td><strong>African American</strong></td>
<td>4 (10%)</td>
<td>1(8%)</td>
<td>3(11%)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>93.8 (21.2)</td>
<td>102.2 (23.1)</td>
<td>89.8 (19.4)</td>
</tr>
<tr>
<td><strong>Duration of HF (months)</strong></td>
<td>95.0 (88.4)</td>
<td>95.0 (61.0)</td>
<td>95.0 (101.1)</td>
</tr>
<tr>
<td><strong>Ischemic/Non-ischemic</strong></td>
<td>29(73%) /11(28%)</td>
<td>9(69%) / 4(31%)</td>
<td>20(74%) / 7(26%)</td>
</tr>
<tr>
<td><strong>NYHAClass</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>24 (60%)</td>
<td>7 (54%)</td>
<td>17 (63%)</td>
</tr>
<tr>
<td>III</td>
<td>16 (40%)</td>
<td>6 (46%)</td>
<td>10 (37%)</td>
</tr>
</tbody>
</table>
## Background Medical Therapy for All Patients

<table>
<thead>
<tr>
<th>Drug Classes</th>
<th>Drug</th>
<th>Placebo</th>
<th>GGF2 (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose</td>
<td>0</td>
<td>0.007 0.021 0.063 0.189 0.378 0.756 1.512</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>13</td>
<td>4 4 4 4 4 4 3</td>
</tr>
<tr>
<td></td>
<td>M/F</td>
<td>12M/1F 2M/2F 4M/0F 2M/2F 3M/1F 3M/1F 4M/0F 3M/0F</td>
<td></td>
</tr>
<tr>
<td>Drug Classes</td>
<td>ALL</td>
<td>Avg Age</td>
<td>54.7 52 58.5 56.8 65.3 58.5 59 61</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>39</td>
<td>12</td>
<td>4 4 4 4 4 4 4 3</td>
</tr>
<tr>
<td>ACE-Inhibitors/ARBs</td>
<td>30</td>
<td>9</td>
<td>3 3 3 3 3 3</td>
</tr>
<tr>
<td>Diuretics</td>
<td>34</td>
<td>10</td>
<td>4 3 4 4 4 3 3</td>
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<tr>
<td>Aldosterone Antagonists</td>
<td>26</td>
<td>5</td>
<td>4 1 3 4 3 3 3</td>
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<tr>
<td>Statins</td>
<td>32</td>
<td>11</td>
<td>3 4 3 3 3 2 3</td>
</tr>
<tr>
<td>Aspirin</td>
<td>30</td>
<td>11</td>
<td>4 4 3 3 3 3 3</td>
</tr>
<tr>
<td>Clopidogrel (other anti-platelet)</td>
<td>8</td>
<td>2</td>
<td>0 1 1 2 0 0 2</td>
</tr>
<tr>
<td>Coumadin/Heparin/Direct Thrombin</td>
<td>18</td>
<td>7</td>
<td>1 3 1 3 1 1 2</td>
</tr>
<tr>
<td>Amiodarone/Other Antiarrhythmic</td>
<td>9</td>
<td>4</td>
<td>0 2 0 1 1 1 0</td>
</tr>
<tr>
<td>Digoxin</td>
<td>18</td>
<td>5</td>
<td>4 3 2 1 2 0 1</td>
</tr>
<tr>
<td>Vasodilator</td>
<td>5</td>
<td>2</td>
<td>1 0 0 1 0 1 0</td>
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## Treatment Emergent Adverse Events (TEAEs)

<table>
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<tr>
<th>GGF2 (mg/kg) Dose</th>
<th>Placebo</th>
<th>0.007</th>
<th>0.021</th>
<th>0.063</th>
<th>0.189</th>
<th>0.378</th>
<th>0.756</th>
<th>1.512</th>
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<tbody>
<tr>
<td>Patients with Any TEAEs</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total TEAEs</strong></td>
<td><strong>6</strong></td>
<td><strong>12</strong></td>
<td><strong>7</strong></td>
<td><strong>4</strong></td>
<td><strong>16</strong></td>
<td><strong>13</strong></td>
<td><strong>13</strong></td>
<td><strong>10</strong></td>
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<tr>
<td>Nervous System - headache</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
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<td>2</td>
<td></td>
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<tr>
<td>Nervous System - other</td>
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<td>2</td>
<td>2</td>
<td>3</td>
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<tr>
<td>GI</td>
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<td>2</td>
<td>2</td>
<td>3</td>
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<td>Administration Site</td>
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<td>Respiratory, Thoracic</td>
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<td>2</td>
<td>1</td>
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<td></td>
<td>0*</td>
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<td>Investigations</td>
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<td>Vascular</td>
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<td>Infections</td>
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<td>Musculoskeletal</td>
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<td>Cardiac - Angina pectoris</td>
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<td>Cardiac - HF</td>
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<tr>
<td>Cardiac - flutter</td>
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<td></td>
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<tr>
<td>Metabolism and</td>
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<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td>1**</td>
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<td>Renal and Urinary</td>
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<td>1**</td>
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<td>1**</td>
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<td>Dermal</td>
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<td>Ear and Labyrinth</td>
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<td>Eye</td>
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<tr>
<td>Hepatobiliary - Hy's Law</td>
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<td></td>
</tr>
</tbody>
</table>

* SGOT, SGPT and bilirubin reached Hy’s Law criteria by day 2 and began to resolve on day 4, returning to baseline by day 14.

** Uroepithelial carcinoma detected 3 months after dosing due to hematuria, this condition was likely present prior to dosing based on microscopic hematuria noted at baseline.
Change in EF Following Single Dose of GGF2 or Placebo

Baseline EF for Placebo/Treatment cohorts: ~ 29%

Single infusion of GGF2 or Placebo at Day 0
Phase 1 Study

- Phase I complete with acceptable safety and tolerability through 0.75 mg/kg
- Adverse events:
  - Most common: headache
  - Most serious: hepatotoxicity (observed at highest dose level in one patient)
    - Transient and reversible
    - Met Hy’s Law criteria
    - Dose-limiting toxicity
- A single dose of GGF2 treatment resulted in an apparent dose-responsive trend toward improved cardiac function and decreased internal LV dimensions
- Apparent dose-response relationship observed on markers of cardiac function, consistent with preclinical in vivo models
GGF2 Next Steps

Anthony Caggiano, MD, PhD
VP, Research & Development
Second Phase 1 Clinical Trial in Heart Failure

- Study of PK interaction
  - Effect of single IV infusion of GGF2 or placebo on midazolam PK in patients with heart failure
- Three dose levels for tolerability and several exploratory measures of efficacy
  - Ejection fraction
  - Measures of endurance
- Estimated enrollment: 28 patients, 18-75 years old
- Trial initiated in September 2013
- Estimated study completion date: Q1 2015
Beyond Heart Failure
Potential Neurological Applications

Stroke

Peripheral Nerve Damage
Damage to the spinal cord that is caused by trauma, such as a motor vehicle accident, fall or sports injury.

- Vehicular: 36.50%
- Falls: 28.50%
- Violence: 14.30%
- Sports: 9.20%
- Other/Unknown: 11.40%

National Spinal Cord Injury Statistical Center; February 2013
• Annual incidence of SCI, not including those who die at the scene of the accident, is approximately 40 cases per million in the U.S.
  – Each year there are approximately 12,000 new cases each year
  – There are between 238,000 and 332,000 people in the United States living with a spinal cord injury; ~2 million people worldwide
• There are no FDA-approved therapies indicated to treat, mitigate, or reverse SCI
AC105 Features

- Proprietary neuroprotective magnesium formulation
- Intravenous formulation administered hours after the injury
- Intended for ER setting
• Divalent cations (Ca and Mg) help maintain cell membrane integrity
• Mg controls excitability particularly at the NMDA channel
• Mg is lost from injured central nervous system
• Increased Mg concentration is protective in multiple laboratory models
Effect of Dose in SCI Model

Kwon BK, et al.
Journal of Neurotrauma 26:1379-1393 (August 2009)
• Preclinical studies found reduction of lesion size and improvement of functional outcome in SCI
• Phase 1 study completed
  – Planned dose for Phase 2 study was well tolerated
• Fast Track designation
• U.S. Department of Defense (DOD) $2.67 million contract in partial support of the trial
Phase 2 MAGNIFY Trial

- Double-blind, randomized and placebo controlled study
- 6 intravenous doses over 30 hours
- Primary outcome measure: Safety and tolerability
- Secondary measures:
  - PK parameters of AC105
  - Neurological outcome
  - Imaging (MRI)
  - Biomarkers of tissue injury
- 40 patients; 18-65 years of age
rHlgM22: A Novel Investigational Compound to Enhance Remyelination

Anthony O. Caggiano, MD, PhD
VP, Research & Development
IgM antibodies were identified by Dr. Moses Rodriguez at Mayo Clinic, Rochester, MN

- Naturally occurring IgM antibody
- Binds CNS myelin
- Shown to promote remyelination in animal models
- In development as investigational therapeutic for multiple sclerosis (MS)
Remyelination & rHlgM22

Moses Rodriguez, MD
Mayo Clinic
Current Therapies for MS

• Therapies approved by FDA to reduce relapses act by decreasing inflammation

• Major goal for MS treatment is to restore myelination, which is the principal pathological process resulting in neurologic deficits

• Remyelinating therapies are the next potential major advance in MS

• Recombinant human IgM22 effective in promoting remyelination in preclinical models
Mice inoculated with spinal cord homogenates
  - Antibody purified from these mice shown to bind to oligodendrocytes and promote remyelination
  - Found that the antibodies were germ-line or naturally occurring antibodies

Similar antibodies identified from human sera which promote remyelination in animal models

Mayo Clinic and Acorda Therapeutics advanced candidate into preclinical development with additional funding from the Hilton Foundation
Identifying Human Antibodies

- Mayo Clinic Hematology sera bank with 125,000+ samples archived over 45 yrs
- Screen sera for IgG or IgM peak >20mg/ml
  - lympho-proliferative disorders
  - (multiple myeloma, lymphoma monoclonal gammopathy)
- A few hundred shown to bind to cells and CNS tissue
- 6 candidate human IgMs from 200 screened were screen for ability to promote in vivo repair
- Two human IgMs promote remyelination
Lead Antibody - rHlgM22

- rHlgM22 was selected as the lead antibody
- In development as therapeutic for MS
- Research collaboration with Mayo Clinic has resulted in a program with efficacy, safety and manufacturing data

Human IgM antibody with mouse J chain

Expressed in F3B6 cells (Mitsunaga et al.)
Both serum purified (sHIgM22) and recombinant (rHIgM22) antibodies selectively bind to myelin in brain sections.

Tissue binding has been explored in mouse, rabbit, monkey, baboon and human tissues. Only CNS myelin shows binding. rHIgM22 was not shown to bind to any other tissue.
Cross Species Reactivity

rHlgM22 binding to oligodendrocytes of different species
Theiler’s Murine Encephalomyelitis Virus Model

Mouse Model

After infection mice develop demyelinated lesions in spinal cord and brain

Progressive disease course eventually leading to death
TMEV Model Histopathology

Uninfected mouse with normal myelin

Examples of typical demyelinated lesion in TMEV at low (left circle) and high (right) magnification
Two IgM antibodies (IgM22 and IgM46) were shown to promote remyelination in the TMEV model.
rHlgM22 in TMEV Model of MS in Mice

- Mice are infected with TMEV
- Treatment begins after mice begin to develop symptoms which is typically several weeks
- Treatments
  - Various dose levels
  - One or two treatments
- Assessed remyelination histologically
- Assessed motor activity
rHlgM22 Stimulates Remyelination

Areas from cords of mice showing evidence of remyelination

* P < 0.05
Mice were treated with rHlgM22 and then cords were assessed for demyelination and remyelination at 5 or 10 weeks after treatment.

(Warrington et al., 2002)
Summary of rHIgM22 Results in TMEV

- rHIgM22 was effective at relatively low doses
- A single treatment was as effective as multiple treatments over several months
- rHIgM22 was effective in the presence of methylprednisolone
  - Reduced demyelination
  - Enhanced remyelination
Spontaneous activity measured in activity box after a single treatment with rHlgM22

Mice treated 30 days after TMEV infection with 1 mg MP twice a week, with or without a single 0.5 mg bolus of rHlgM22.

(Rodriguez et al., 2009)
rHlgM22 Selectively Accumulates in Active Diseased Brain

MRI of TMEV mice with USPIO labeled rHlgM22 (left) or control antibody (right)

- T1-weighted
- Spin-Echo
- 3D acquisition
- Fully isometric
- Resolution 180 mm
- 7 T / Axial slice

Chronic TMEV-infected mice: 48 hr after rHlgM22 administration
Treatment with rHlGm22 Reduces T2-MRI Lesion Size
Remyelination in a Spinal Cord Lesion Identified by T2-MRI
Mice were treated 6 months after infection.

Treated for 5 weeks with PBS.

Lesion volume assessed by MRI before and after treatment.

PBS treated animals had a 13.6% increase in lesion volume.
Mice were treated 6 months after infection
- Treated for once with rHlgM22
- Lesion volume assessed by MRI before and after treatment
- rHlgM22 treated animals had a 40.6% decrease in lesion volume
IgM Treatment Increases NAA

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>5wk vs. before</th>
<th>10wk vs. before</th>
</tr>
</thead>
<tbody>
<tr>
<td>rHlgM22</td>
<td>p=0.041</td>
<td>p=0.0166</td>
</tr>
<tr>
<td>sHlgM42</td>
<td>p=0.047</td>
<td>p=0.023</td>
</tr>
<tr>
<td>sHlgM12</td>
<td>p=0.004</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>sHlgM39</td>
<td>p=0.883</td>
<td>p=0.188</td>
</tr>
<tr>
<td>Saline</td>
<td>p=0.0262</td>
<td>p=0.006</td>
</tr>
</tbody>
</table>
rHlGm22 Induces Elevation of Intracellular Calcium Concentration
• Oligodendrocyte calcium response
  Delayed from antibody binding
  Extracellular Ca2+ through AMPA channels
  Antigen binding domain of IgM induces response

• Astrocyte calcium response
  Immediate upon antibody binding
  Intracellular Ca2+ through PLC
  Fragmentation of IgM

• Lipid antigen for remyelination promoting antibodies?
  Lipid microdomains
  Lipid second messengersabrogates response
mAbs Promote Myelin-related Gene Expression

<table>
<thead>
<tr>
<th>MYELIN GENE</th>
<th>% of Control Expression</th>
<th>T TEST</th>
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</thead>
<tbody>
<tr>
<td>Proteolipid protein</td>
<td>137 ± 15</td>
<td>p = 0.05</td>
</tr>
<tr>
<td>DM-20 PLP</td>
<td>147 ± 3</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>Myelin basic protein</td>
<td>124 ± 0.4</td>
<td>p = 0.03</td>
</tr>
<tr>
<td>Myelin-associated glycoprotein</td>
<td>107 ± 9</td>
<td>p = 0.3</td>
</tr>
<tr>
<td>Myelin oligodendrocyte basic protein</td>
<td>191 ± 19</td>
<td>p = 0.005</td>
</tr>
<tr>
<td>Myelin oligodendrocyte glycoprotein</td>
<td>140 ± 17</td>
<td>p = 0.04</td>
</tr>
</tbody>
</table>

Data are shown as percent of myelin gene levels measured in infected animals treated only with PBS. Values shown are means of three independent experiments ± SEM.

SJL/J mice were treated with rHlgM22 180 days after TMEV infection. Gene expression was measured from harvested spinal cords at day 26 post-treatment.

(Howe et al., 2004)
IgM Mediated Membrane Domain Clustering

\[ \text{Survival} \uparrow, \text{Differentiation} \downarrow, \text{Proliferation} \uparrow \]

\[ \text{Caspase-3} \downarrow, \text{Caspase-9} \downarrow, \text{PARP} \downarrow \]

IgM Mediated Membrane Domain Clustering

IgM

Sulfated Lipid

PDGFR

\( \alpha \beta 3 \) Integrin
rHlGm22 Development Status

Anthony Caggiano, MD, PhD
VP, Research & Development
### Phase 1 Trial in People with MS

**ClinicalTrials.gov**

*A service of the U.S. National Institutes of Health*

<table>
<thead>
<tr>
<th>#</th>
<th>Status</th>
<th>Study Title</th>
<th>Condition</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Recruiting</td>
<td>An Intravenous Infusion Study of rHlgM22 in Patients With Multiple Sclerosis</td>
<td>Multiple Sclerosis</td>
<td>Drug: rHlgM22 first dose; Drug: rHlgM22 second escalated dose; Drug: rHlgM22 third escalated dose; Drug: rHlgM22 fourth escalated dose; Drug: rHlgM22 fifth escalated dose; Drug: rHlgM22 sixth escalated dose</td>
</tr>
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</table>
rHlgM22 Phase 1 Trial in MS

This is a Phase I, multi-center, double-blind, randomized, placebo-controlled, dose-escalation study designed to evaluate safety, tolerability, PK, & immunogenicity of single (IV) administrations of rHlgM22 in patients with all clinical presentations of MS

**Inclusion:**
Patients with all forms of MS on a stable regimen of at least 3 months
- Informed consent
- Inpatient X 2 days
- MRI Possible

**Exclusion:**
Various limitations related to unstable disease, certain past medications and/or therapies

**Study Type:**
Single ascending dose
The rHlgM22 Phase 1 Trial Structure

PK, Imaging (MRI) & Molecular Assessments
Clinical Assessments
The rHlgM22 Phase 1 Trial Dose Levels

Cohort: 8 Active + 2 Placebo

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Dose</th>
</tr>
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<tbody>
<tr>
<td>Level 5</td>
<td>4 % NOAEL</td>
</tr>
<tr>
<td>Level 4</td>
<td></td>
</tr>
<tr>
<td>Level 3</td>
<td></td>
</tr>
<tr>
<td>Level 2</td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>1/20 of 1 % NOAEL</td>
</tr>
</tbody>
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NOAEL is the maximum dose at which no adverse events were observed in the most sensitive animal model.
The rHIgM22 Phase 1 Trial - Considerations

End Original Study

Level 4
Level 5
Level 6

6th Cohort
Expanded Study
More Clinical Measures
+
Exploratory Biomarkers
An Expanded Cohort Incorporating Biomarkers

PK, Imaging (MRI) & Molecular Assessments

Clinical Assessments
• Current Phase 1 trial is being conducted in stable MS patients with or without current MS medications

• The expanded cohort is designed to:
  – Follow patients over longer period
  – Produce evidence of biological activity
  – Expand functional measures, imaging and biomarkers

• Novel therapy with potential to repair lesions and improve function