ASH
Complement Factor D Symposium
Sunday, December 6, 2015 | 8:00 – 10:00 pm
Complement Symposium Agenda

01 Welcome
Milind Deshpande, Ph.D.
President & CEO, Achillion

02 Complement Immuno-biology
Scott Barnum, Ph.D.
Professor of Microbiology, University of Alabama at Birmingham

03 Complement and Infection: Relative Risks Associated with Immune Modulation
Peter Densen, M.D.
Professor of Internal Medicine - Infectious Diseases, University of Iowa

04 Small-molecule Factor D Inhibitor: ACH-4471
David Apelian, M.D., Ph.D.
Executive Vice President and Chief Medical Officer, Achillion
Forward-Looking Statements

This presentation includes forward-looking statements about Achillion Pharmaceuticals, Inc. and its business, including, without limitation, statements regarding drug discovery, clinical development, regulatory approval processes, market opportunities, intellectual property, competition, and financial results. All statements other than statements relating to historical matters (including statements to the effect that we “believe,” “expect,” “anticipate,” “plan,” “target,” “intend” and similar expressions) should be considered forward-looking statements. These forward-looking statements are subject to risks and uncertainties that may cause actual events or results to differ materially from our current expectations. These risks and uncertainties are detailed in the "Risk Factors" sections of our annual report on Forms 10-K and 10-Q, and subsequent filings with the SEC.

All forward-looking statements contained in this presentation speak only as of the date hereof, and we undertake no obligation to update any of these statements, except as required by law.
We are rapidly becoming a fully-integrated commercial pharmaceutical company through our highly disciplined, science-driven, and patient-focused approach.

POWERING sustainable, highly-productive discovery engine

DEVELOPING a pipeline of potent and specific complement inhibitors for rare and other diseases

PURSUING best-in-class therapy for HCV through billion-dollar collaboration

FOCUSING on patient needs and marketplace dynamics
SCIENCE DRIVEN. PATIENT FOCUSED.
The Complement System Pipeline
Achillion Complement Program Genesis

Beginning in 2012, original interest in complement was provoked by search for novel anti-bacterial agents, and was facilitated by our expertise in protease inhibitors and small molecule discovery and development.

- Bacteria secrete SSL7 protein, which inhibits MAC formation by binding to C5
- X-ray structure of C5 + SSL7 known
- Idea led to initiation of complement program

Factor D and C5 were evaluated as potential targets

- Factor D prioritized over C5
  - Mechanism-based pharmacological benefits
  - Availability of structural information
  - Early success in determining x-ray structure of enzyme/inhibitor complex
Why Factor D?

- Plays a central role in AP and overall complement activation through amplification loop
- An attractive “control point” for complement activation
- Lowest plasma concentration of all complement components, representing a highly “druggable” target
- Amenable to potent inhibition by small-molecule drugs
- Validated target
- Promising therapeutic target in variety of ultra-rare diseases and serious conditions

We believe factor D and its differentiated MOA could provide improved efficacy, safety and convenience.
Early, rigorous assessment of drug-like properties enhances potential for successful development
# View of Complement-Related Diseases Across a Two-Dimensional Matrix: Disease Prevalence vs. Route of Administration

**Route of Administration**

<table>
<thead>
<tr>
<th>Prevalence*</th>
<th>Oral systemic</th>
<th>Ocular</th>
<th>Inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra rare</td>
<td>PNH</td>
<td></td>
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<tr>
<td>&lt;20K</td>
<td>aHUS</td>
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<tr>
<td></td>
<td>C3g nephropathies</td>
<td></td>
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<tr>
<td>Rare</td>
<td>Lupus nephritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200K</td>
<td>Myasthenia Gravis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td>Multiple sclerosis</td>
<td>Dry AMD</td>
<td>COPD Asthma</td>
</tr>
<tr>
<td>&gt;200K</td>
<td>Rheumatoid arthritis</td>
<td></td>
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</tbody>
</table>

*Partial list of complement-related diseases

**Achillion complement factor D program**
Distinct NCEs specific for each disease group and route of administration
ACHILLION FACTOR D INHIBITORS
Excellent Target Product Profiles

- Orally bioavailable, potent and specific
- Bind to factor D with high affinity resulting in inhibition of alternative pathway (AP)
- Effectively block C3 fragment deposition on cells, in contrast to C5-targeted therapies
- Demonstrate complete suppression of complement activity after oral dosing *ex vivo*
- Safety assessment supports clinical development
- Represent a promising oral therapy for PNH and other complement-mediated diseases
  - Subject of ASH 2015 presentation

ACH-4471 is the first potent, specific, oral factor D inhibitor from the Achillion complement platform.
# Research and Development Pipeline

## Achillion Discovery Engine

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>PROGRAM DELIVERY</th>
<th>INHIBITOR</th>
<th>PHASE</th>
<th>PARTNER</th>
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<tbody>
<tr>
<td><strong>FACTOR D INHIBITOR PLATFORM</strong></td>
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<tr>
<td>PNH and Ultra-rare Diseases</td>
<td>Oral</td>
<td>Factor D</td>
<td>1</td>
<td><img src="achillion.png" alt="ACHILLION Logo" /></td>
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<tr>
<td>Dry AMD</td>
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<td>COPD</td>
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<table>
<thead>
<tr>
<th><strong>HEPATITIS C VIRUS</strong></th>
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<tbody>
<tr>
<td>HCV</td>
<td>Oral</td>
<td><strong>odalasvir + simeprevir + ALS-335</strong></td>
<td>2</td>
<td><img src="janssen.png" alt="janssen Logo" /></td>
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<td>HCV</td>
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<td>Highly water soluble inhibitors</td>
<td>Potential &gt;3 month delivery</td>
<td>Inhalation</td>
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December 2015

ASH Complement Factor D Symposium
Factor D in Paroxysmal Nocturnal Hemoglobinuria (PNH)

- Goal of providing consistent and potent inhibition of complement for all PNH patients
- Inhibition of hemolysis in patients carrying C5 mutation (Arg885His)
  - Ability to treat non-responders to C5 monoclonal antibody treatment
- Prevention of extravascular hemolysis mediated by C3b opsonization
  - C5 inhibition does not prevent opsonization-related hemolysis
Patient-Focused Opportunities

A DISRUPTIVE APPROACH TO TREATING COMPLEMENT-MEDIATED DISEASES

IMPROVE TREATMENT OUTCOMES based on a differentiated mechanism of action

ORAL ADMINISTRATION could significantly alter treatment landscape

Pursue therapeutic indications for MULTIPLE DEVASTATING DISEASES

WORK TO EXPAND THERAPEUTIC OPTIONS to address the needs of patients
PURSUING BEST-IN-CLASS ANTIVIRAL THERAPY FOR HCV

Achillion – Janssen Worldwide HCV Collaboration
Achillion — Janssen Worldwide HCV Collaboration

Collaboration with Janssen creates the opportunity for a best-in-class regimen

<table>
<thead>
<tr>
<th>NS5A inhibitor</th>
<th>NS5B polymerase inhibitor (nuc)</th>
<th>NS3/4A protease inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achillion - Janssen</td>
<td>odalasvir (ACH-3102)</td>
<td>ALS-335</td>
</tr>
<tr>
<td>Gilead</td>
<td>GS-5816</td>
<td>sofosbuvir</td>
</tr>
<tr>
<td>Merck</td>
<td>MK-8408</td>
<td>MK-3682</td>
</tr>
</tbody>
</table>

Janssen’s aims to initiate Phase 3 development by early 2017

Odalasvir (ACH-3102) + Sofosbuvir (Phase 2 Proxy Study)

6- & 8-week Treatment Arms: Interim Efficacy Results

<table>
<thead>
<tr>
<th>% of Patients</th>
<th>N=10/12</th>
<th>N=12/12</th>
<th>N=12/12</th>
<th>N=11/11*</th>
<th>N=12/12</th>
<th>N=12/12</th>
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<tbody>
<tr>
<td>RVR 8-week treatment</td>
<td>83%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>ETR 8-week treatment</td>
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<tr>
<td>SVR4</td>
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<tr>
<td>SVR8</td>
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<tr>
<td>SVR12</td>
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<tr>
<td>SVR24</td>
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6-week treatment

<table>
<thead>
<tr>
<th>% of Patients</th>
<th>N=15/18</th>
<th>N=18/18</th>
<th>N=18/18</th>
<th>N=18/18</th>
</tr>
</thead>
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<td></td>
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<tr>
<td>SVR12</td>
<td></td>
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</table>

*One patient was unavailable for HCV quantification at Week 8 post-treatment (SVR8).
Achillion-Janssen HCV Collaboration

- Creates potentially best-in-class combined pipeline to benefit HCV patients
- Access global development and commercial infrastructure fully funded by Janssen
- Attractive economics, including royalties from the mid-teens to low-twenties
- Potentially accelerates time to participate in worldwide HCV market
### Achillion Financial Summary:
#### Capitalization and Ownership

<table>
<thead>
<tr>
<th>Balance Sheet Metrics</th>
<th>As of 9/30/2015</th>
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<tbody>
<tr>
<td>Cash And Equivalents</td>
<td>$476 million</td>
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<tr>
<td>Debt Obligations</td>
<td>$0.5 million</td>
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<tr>
<td>Shares Outstanding</td>
<td>136.4 million</td>
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<table>
<thead>
<tr>
<th>Top Shareholders†</th>
<th>Position</th>
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<tbody>
<tr>
<td>Johnson &amp; Johnson Development Corp.</td>
<td>18.4 million (13%)</td>
</tr>
<tr>
<td>RA Capital</td>
<td>11.3 million (8%)</td>
</tr>
<tr>
<td>Wellington Management</td>
<td>10.6 million (8%)</td>
</tr>
<tr>
<td>Point72 Asset Management</td>
<td>10.0 million (7%)</td>
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<tr>
<td>Fidelity Management &amp; Research</td>
<td>8.9 million (7%)</td>
</tr>
<tr>
<td>Orbimed Advisors</td>
<td>8.1 million (6%)</td>
</tr>
<tr>
<td>Janus Capital Management</td>
<td>8.0 million (6%)</td>
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<tr>
<td>Blackrock Institutional</td>
<td>7.6 million (6%)</td>
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<tr>
<td>Vanguard Group</td>
<td>7.6 million (6%)</td>
</tr>
<tr>
<td>State Street Global</td>
<td>5.0 million (4%)</td>
</tr>
<tr>
<td>T. Rowe Price</td>
<td>4.5 million (3%)</td>
</tr>
</tbody>
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† Based upon most recent SEC filings and confirmed positions.
Achillion: Positioned for Success

“Understanding the binding of factor D at the molecular level allows us to exquisitely target and inhibit a critical control point in the alternative pathway within the complement cascade.”

ROBUST financial position allows Achillion to advance programs through value inflections points and to commercialization.

HIGH VALUE targets for complement inhibition aimed at addressing patient needs for both ultra rare and broader diseases.

PURSUING best-in-class therapy for HCV through billion-dollar collaboration with Janssen.

INNOVATION taking place throughout the organization aimed at meeting the needs of patients and changing marketplace dynamics.
Welcome
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David Apelian, M.D., Ph.D.
*Executive Vice President and Chief Medical Officer, Achillion*
Scott Barnum, PhD

University of Alabama at Birmingham

- Professor of Microbiology, (secondary appointments in Neurology and Rheumatology)
- Research: Complement, adhesion molecules, innate immunity, neurodegenerative diseases
- Post Doctoral Fellowship: Scripps Institute
  - Genomic organization of Complement genes
- Ph.D. : University of Alabama, Birmingham
  - Biosynthesis and catabolism of Complement Factor D
Peter Densen, MD

Carver College of Medicine
University of Iowa

• Executive Dean of Carver College of Medicine at University of Iowa.
• Research: molecular basis of inherited complement deficiencies and the roles of the complement system in the pathogenesis of infections
• MD: Johns Hopkins
• Residency (Internal Medicine): Johns Hopkins
• Fellowship (Infectious Diseases): University of Virginia
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President & CEO, Achillion

Complement Immuno-biology
Scott Barnum, Ph.D.
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Complement Symposium
Complement Immunobiology

Scott Barnum, Ph.D.
Department of Microbiology
University of Alabama at Birmingham
Complement is an ancient component of the immune system
- Complement-like proteins are found in primitive organisms

Simple organisms have a rudimentary Alternative Pathway
- targets pathogen for removal by white blood cells

Recognizes pathogen associated molecular patterns (PAMPs)
- chemical structures found on pathogens and not on host cells
- evolved to recognize pathogens targeted by other immune proteins such as antibodies and C-reactive protein
Complement:
innate immune host defense

- Critical component of the innate immune system
- First line of defense against invading pathogens including bacteria, viruses & parasites
- Acts immediately on infection/trauma to eliminate pathogens and aid in tissue repair
- Nearly 60 proteins and several activation pathways are now known to comprise the complement system
Complement: a working definition

Complement:

- **A group of sequentially reacting proteins** – complement activation is a cascade of cleavage events, similar to the coagulation system.

- **Requires activation** to provide host defense against pathogens – normally is “inactive”.

- **Mediates numerous biological reactions important in host defense** – a multi-pronged approach to labeling pathogens, focusing innate immune responses and killing pathogens.
Complement – Constitutively Produced

- Soluble proteins produced primarily by hepatocytes, found in blood and essentially all body fluids
- Regulatory proteins expressed on nearly all cell types to protect against excessive or inappropriately targeted complement activity
- Nearly all cell types can produce complement in response to infection, trauma or autoimmune-induced inflammation
Complement: Activation vs. Regulation

**Activation**
- C3(H2O)/C3b
- Factor D  Factor B
- Properdin
- MASP-1, 2, 3  MBP
- Ficolin  Collectins
- C1  C2  C3  C4
- C5  C6  C7  C8  C9

**Regulation**
- C1-INH  C4BP
- Factors H and I
- Vitronectin
- Carboxypeptidases
- CR1  CD59
- DAF (CD55)
- CD46 (MCP)  CR1g
COMPLEMENT PATHWAYS

CLASSICAL  MBP/Ficolin  ALTERNATIVE

C3a  C3  C3b

Inflammation  Phagocytosis

C5a  C5  C5b + C6-C9

Terminal  Cell Lysis
Complement Activation

Classical Pathway:

• Activated by Ag-Ab complexes, CRP, damaged tissues
• Couples innate and adaptive systems
• Targets extracellular pathogens of diverse types, important in opsonophagocytosis

Lectin Pathway:

• Activated by pathogen-specific carbohydrates (sugars)
• Couples to the classical pathway, employs structurally similar protein components
• Targets pneumococcus and other bacteria
Complement Activation

**Alternative Pathway:**

- Activated through “tickover”, PAMPS such as LPS, damaged tissues
- Primed to respond quickly and vigorously to pathogens or injury, (amplification loop)
- Targets extracellular pathogens of diverse types
- Dysregulation contributes to debilitating and life-threatening disease
Complement Host Defense Functions

**C3**
- C3a: Chemotaxis, Inflammation, Antimicrobial
- C3b: Opsonization, Neutralization, B cell activation

**C5**
- C5a: Chemotaxis, Inflammation
- C5b: Lytic complex formation

**Convertases**
Tickover: $\text{C3}(\text{H}_2\text{O})$ and $\text{C3b}$ Generation

- $\text{C3}$ Thio-ester exposed
- $\text{C3}$ convertase
- $\text{C3b}$
- $\text{C3 (H}_2\text{O)}$ FB Binding Site Exposed
- $\text{C3a}$
Complement Regulation

• Regulation ≈ Activation (based on activator type and amount)

• Inhibitory proteins to control early activation

• Regulatory proteins limit convertase activity (short $t_{1/2}$)

• Carboxypeptidases inactivate the anaphylatoxins

• Inhibitory proteins to modulate MAC formation
Failure to Regulate Complement…

- Unchecked convertase activity – mutations, autoantibody
- Inappropriate targeting of host tissues – C4b, C3b, iC3b
- Chemoattraction/activation of myeloid cells - C5a, C3a
- Leaky vasculature/edema - C5a, C3a
- Localized or systemic acute phase response - C5a, C3a
- Cellular destruction – tissue/organ dysfunction - MAC
**Alternative Pathway & Human Disease**

- Animal models validate the alternative pathway as a key contributor to inflammatory and autoimmune disease.

- Inhibition of alternative pathway activity protects in:
  - Lupus nephritis
  - Rheumatoid arthritis
  - Ischemia/reperfusion injury
  - Spinal cord injury
  - Demyelinating disease
  - Traumatic brain injury
  - Asthma
  - Macular degeneration
  - Glomerulonephritis
  - Atypical hemolytic-uremic syndrome
  - PNH
Alternative Pathway: Age-Related Macular Degeneration

- Genetic variants in alternative pathway proteins (C3, FB, FH) are associated with AMD risk
- AMD patients have elevated plasma levels of AP proteins (FD, FB, C3a & others)
- C3, FD & FB are present in the vitreous and Bruch’s membrane in eyes of dry AMD patients
- AP activation occurs in a disease-stage specific fashion
Alternative Pathway: Paroxysmal Nocturnal Hemoglobinuria

- Characterized by deficiency of complement regulatory proteins CD55 and CD59

- Leads to red cell lysis through alternative and terminal pathway dysregulation

- Patients have both C3d and MAC deposition on RBCs

- Regulation of the MAC with eculizumab provides only partial protection, need to prevent AP deposition of C3 on RBCs
• Mutations in C3, FB, FH are associated with development of C3 glomerulonephritis
• Patients have uncontrolled activation of the alternative pathway in the fluid phase and on glomerular cell surfaces and the glomerular basement membrane
• Results in irreversible kidney damage
Alternative Pathway: Atypical Hemolytic Uremic Syndrome

- Characterized by uncontrolled activation of the alternative pathway
- Loss of function mutations (FH, FI, CD46) or gain of function mutations (C3, FB)
- Autoantibodies to FH account for 10% of complement-mediated aHUS
- Acute kidney injury is the classic sign of disease
Factor D - AP Rate-Limiting Enzyme

- Complement factor D, a serine protease required for activation of the complement alternative pathway
- Factor B is the only known substrate
- Lowest plasma concentration of all complement proteins
- Primary synthetic site is the adipocyte
- High synthetic rate, catabolized in the kidney

Factor D bound to Factor B and C3b
Factor D – Drives the Amplification Loop

- Cleaves Factor B to generate the C3 convertase
- Each C3 cleavage generates a new C3 convertase

- Thousands of C3b molecules produced in minutes
- Contributes to opsonization and formation of the MAC
Plasma Concentration of Factor D: Enhances therapeutic target value

<table>
<thead>
<tr>
<th>Complement Protein</th>
<th>Molecular Weight</th>
<th>Plasma Concentration (µg/ml)</th>
<th>Plasma Concentration (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor D</td>
<td>24,000</td>
<td>2</td>
<td>0.083</td>
</tr>
<tr>
<td>C5</td>
<td>190,000</td>
<td>75</td>
<td>0.4</td>
</tr>
<tr>
<td>C3</td>
<td>185,000</td>
<td>1200</td>
<td>6.49</td>
</tr>
</tbody>
</table>
Overview

• Complement is an important contributor to innate immune responses to invading pathogens

• There are several activation pathways but the alternative pathway is primed to respond quickly and vigorously (amplification loop)

• Dysregulation of complement, especially the AP, underlies the pathophysiology of many chronic and debilitating diseases

• Factor D as the rate limiting enzyme of the AP represents an ideal therapeutic target for many complement-mediated diseases
Welcome
Milind Deshpande, Ph.D.
President & CEO, Achillion

Complement Immuno-biology
Scott Barnum, Ph.D.
Department of Microbiology, University of Alabama at Birmingham

Complement and Infection: Relative Risks Associated with Immune Modulation. Peter Densen, M.D.
Professor of Internal Medicine - Infectious Diseases, University of Iowa

Small-molecule Factor D Inhibitors: ACH-4471
David Apelian, M.D., Ph.D.
Executive Vice President and Chief Medical Officer, Achillion
Complement and Infection: Relative Risks Associated with Immune Modulation

Peter Densen, MD
Division of Infectious Diseases
Department of Internal Medicine
University of Iowa

December 6, 2015
The Complement System: Simplified Organization and Function

**CLASSICAL**

C3a  ↦  C3  →  C3b  

**LECTIN**

**ALTERNATIVE**

C5a  ↼  C5  →  MAC

- Complement dependent bacterial killing
- Opsonophagocytic killing

**Phagocytosis**

**Bactericidal Activity**
Genetic Complement Deficiencies Inform Us About Infectious Risks

Comparison of the frequency of occurrence of *Neisseria sp.*, *S. pneumonia*, and *H. influenzae* infections in patients with complement deficiencies

<table>
<thead>
<tr>
<th>Deficiency (no. of Homozygotes)</th>
<th>No. of patients (%) with:</th>
<th></th>
<th></th>
<th>Total (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neisseria sp.</td>
<td>S. Pneumoniae</td>
<td>H. influenzae</td>
<td></td>
</tr>
<tr>
<td>C1, C4, C2 (161)</td>
<td>9 (5.6)</td>
<td>20 (12.4)</td>
<td>8 (5.0)</td>
<td>32 (20)</td>
</tr>
<tr>
<td>C3, I, H (46)</td>
<td>17 (37)</td>
<td>12 (26)</td>
<td>2 (4.4)</td>
<td>25 (54)</td>
</tr>
<tr>
<td>P, D (57)</td>
<td>25 (44)</td>
<td>2 (3.5)</td>
<td>2 (3.5)</td>
<td>29 (51)</td>
</tr>
<tr>
<td>C5–9 (267)</td>
<td>151 (57)</td>
<td>2 (0.8)</td>
<td>0 (0)</td>
<td>150 (56)</td>
</tr>
<tr>
<td>Total (531)</td>
<td>202 (38)</td>
<td>36 (6.8)</td>
<td>12 (2.3)</td>
<td>236 (44)</td>
</tr>
</tbody>
</table>

$^a$Total patients with infection caused by any of the three specified encapsulated organisms.

Each patient is counted only once.

The C5 Story: Genetic Deficiency

- Increased risk for infections with *N. meningitidis*
- Similar risk for any late complement deficiency (C5 – C9)
- Of 27 patients reported in two review articles
  - 19 had infections with *N. meningitidis* (70%)
  - An additional 2 patients had meningitis, but with an unknown organism
- Approximately 4.0 cases per 100 patient years
The C5 Story: Take-aways from C5 Blocking Therapy

- The US incidence of meningococcal infection is 0.15/100,000
  - Risk ↑ 8,000 – 14,000X in terminal complement deficiencies
  - Risk ↑ 2,000X by eculizumab treatment (post-vaccination)
- Incidence of meningococcal infections

<table>
<thead>
<tr>
<th></th>
<th>Incidence of meningococcal infection (cases per 100 patient years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital C5 deficiency</td>
<td>4.0</td>
</tr>
<tr>
<td>Pharmacologic C5 inhibition (eculizumab) with prior vaccination</td>
<td>0.31 – 0.83</td>
</tr>
</tbody>
</table>

*Vaccination appears to reduce the risk of meningococcal infection ~ 5-8 X in patients on eculizumab treatment*
Evolutionary Biology of Complement Pathways

ALTERNATIVE

C3 → C3b → C3bBb → C3

Phagocytosis

B → C3b

Factor D

C3bBb

Cell Lysis

Bacterium

C5 → C5a

C3a → C3b
Evolutionary Biology of Complement Pathways

- LECTIN
- C3 → C3b
- C3a
- C5 → C5a → MAC
- Phagocytosis
- Cell Lysis
- Bacterium
- MBL
Evolutionary Biology of Complement Pathways

CLASSICAL

C3a ← C3 → C3b

C5a ← C5 → MAC → Cell Lysis

Phagocytosis

Bacterium

IgG
## Evolutionary Biology of Complement Pathways

<table>
<thead>
<tr>
<th></th>
<th>Classical Pathway</th>
<th>Lectin Pathway</th>
<th>Alternative Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recognition</strong></td>
<td>Antibody defined epitopes</td>
<td>Shared molecular patterns (e.g., mannose)</td>
<td>None</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>High</td>
<td>Cross reactivity</td>
<td>Non-specific</td>
</tr>
<tr>
<td><strong>Efficiency</strong></td>
<td>High</td>
<td>Modest</td>
<td>Low</td>
</tr>
</tbody>
</table>
Rationale for Factor D Inhibition

What is known about C3 cleavage and C3b deposition

- CP activation leads to C3b deposition that then initiates the AP amplification loop, greatly increasing C3b deposition
  - 80% of C3b deposited on a target occurs via the AP amplification loop
Rationale for Factor D Inhibition

What is known about C3 cleavage and C3b deposition

- CP activation leads to C3b deposition that then initiates the AP amplification loop, greatly increasing C3b deposition
  - 80% of C3b deposited on a target occurs via the AP amplification loop
  - Corollary: 20% of C3b is directly from classical pathway

- Implication: If the AP pathway is blocked there is sufficient C3b deposition via CP alone to support opsonophagocytosis and complement dependent bactericidal activity
The Factor D Story: Reported Clinical Cases of Factor D Deficiency

• Five case series

• All case reports based on an index patient with recurrent or severe infections

• Increased risk for infection with encapsulated organisms
  – In individuals with complete or near-complete deficiency
  – No increased risk of serious infections in heterozygotes

• Other than infections, no trends noted across the case reports
Complement-Mediated Opsonophagocytosis of *E. coli*

**Selective AP vs. CP vs. Terminal Pathway Inhibition**

- Inhibition of terminal pathway reduces phagocytosis in granulocytes, but not in monocytes
- Selective inhibition of AP with anti-factor D antibody has minimal effect on phagocytosis
- Inhibition of AP and CP is required to suppress opsonophagocytosis

Complement-Mediated Lysis of *E. coli*
*Selective AP inhibition vs. Terminal Pathway Inhibition*

- Bactericidal assay
- Factor D inhibitor has little effect on bactericidal serum activity up to the highest concentration evaluated (31 micromolar)
- In contrast, potent inhibition of hemolysis observed at concentrations of 15 nanomolar

---

*Data on file: Achillion Pharmaceuticals, Inc. 2015*
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Incidence of meningococcal infection (cases per 100 patient years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital C5 deficiency</td>
<td>4.0</td>
</tr>
<tr>
<td>Pharmacologic C5 inhibition (eculizumab) with prior vaccination*</td>
<td>0.31 – 0.83</td>
</tr>
<tr>
<td>Congenital factor D deficiency without prior vaccination*</td>
<td>2.1</td>
</tr>
</tbody>
</table>
Summary of Infection Risk with AP Complement Inhibitors

• Specific inhibition of Factor D inhibits only the alternative pathway

• Pathogens remain susceptible to classical pathway-mediated opsonophagocytosis and bactericidal activity

• Infection risk with encapsulated pathogens may be effectively managed with vaccination for *N. meningitidis, S. pneumo and H. flu*
Summary of Infection Risk with AP Complement Inhibitors

• Well characterized infection risk, especially with encapsulated organisms
  – Likely to be no worse, and potentially better than terminal complement inhibitors
  – Strategies for risk mitigation planned, including:
    • Close monitoring and prompt evaluation for signs and symptoms of infection (fever, photophobia)
    • Pre-treatment vaccination
    • Empiric antibiotic coverage during work-up of suspect cases
Parting Thought on Complement and Infection…

“Since the classic studies of Bordet, Erlich, and Wassermann, the concept of complement as an essential part of the mechanism of immunity has progressively been replaced by rather uncertain decision that the classic phenomenon of complement lysis of red cells is a laboratory artifact of no real significance for immunity.”

- Sir Macfarlane Burnet, Nobel laureate

*Cellular Immunology*, 1970.
01 Welcome
   Milind Deshpande, Ph.D.
   President & CEO, Achillion

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   Department of Microbiology, University of Alabama at Birmingham

03 Complement and Infection: Relative Risks Associated with Immune Modulation.
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04 Small-molecule Factor D Inhibitors: ACH-4471
   David Apelian, M.D., Ph.D.
   Executive Vice President and Chief Medical Officer, Achillion
ACH-4471
SMALL MOLECULE
FACTOR D INHIBITORS

David Apelian, MD, PhD, MBA | Executive Vice President & Chief Medical Officer, Achillion
Targeting Complement-Mediated Diseases

Role of Factor D: Simplified View of the Complement System

Complement factor D
- Cleaves factor B, leading to formation of C3 convertase
- Plays an essential role in alternative pathway activation and amplification loop
- Is critical for opsonization and formation of membrane attack complex (MAC)

Receptors
- C3aR; C5aR
- CR1; CR3; CR4
- CR2
- CD55; CD59

Regulators
- Factor H
- Factor P
- Factor I

Inhibitors are potent and highly specific
- Reversible, non-covalent binding to factor D
- 16 inhibitor–enzyme X-ray structures

<table>
<thead>
<tr>
<th>Resolution of inhibitor / fD structure</th>
<th># of X-ray Structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1.2 Å</td>
<td>9</td>
</tr>
<tr>
<td>Resolve H atoms</td>
<td></td>
</tr>
<tr>
<td>1.3–2.0 Å</td>
<td>4</td>
</tr>
<tr>
<td>2.1–2.3 Å</td>
<td>3</td>
</tr>
</tbody>
</table>


*Factor D:ACH-4471 complex at 0.9 Å*
SMALL MOLECULE FACTOR D INHIBITORS
Chemical Structures & Properties

- Synthesized >1000 structurally diverse inhibitors
  - Synthesis guided by high-resolution X-ray structures of inhibitor–enzyme complexes
  - Inhibitors represent 8 distinct chemical modifications that confer a wide range of drug-like properties (permeability, solubility, etc.)
  - At least one X-ray structure for each of the 8 chemical series
  - Deep insight into the molecular recognition of the inhibitors, ability to tune potency
  - >200 inhibitors demonstrate ≤100 nM potency; 40 inhibitors demonstrate ≤10 nM

<table>
<thead>
<tr>
<th>AP Hemolysis IC50 (nM)</th>
<th># of Inhibitors</th>
<th># of Chemical Series Represented</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10</td>
<td>41</td>
<td>6</td>
</tr>
<tr>
<td>&gt;10- ≤25</td>
<td>71</td>
<td>5</td>
</tr>
<tr>
<td>&gt; 25- ≤50</td>
<td>49</td>
<td>8</td>
</tr>
<tr>
<td>&gt;50- ≤100</td>
<td>81</td>
<td>8</td>
</tr>
<tr>
<td>≤100</td>
<td>242</td>
<td>8</td>
</tr>
</tbody>
</table>
Nomination of ACH-4471 for Clinical Development

- Preclinical program for ACH-4471 supports advancement as first small molecule inhibitor of factor D into clinical development
- Highly differentiated approach for treatment of complement-based diseases
  - Specifically targets amplification loop of the complement pathway
- Convenience of oral administration
- Being developed for the treatment of PNH and other ultra-rare diseases

Goal of introducing a disruptive approach to treating complement-mediated diseases with AP-specific inhibition
ACH-4471
Prevents Binding of C3b/Factor B Complex to Factor D

- Mode of action is highly specific for factor D / factor B interaction
- ACH-4471 does not inhibit other endogenous serine proteases
**ACH-4471**

**Lead Complement Factor D Inhibitor Potent Inhibition of Factor D (fD) Proteolytic Activity**

- Inhibitors demonstrate potent inhibition of factor B cleavage
  - Assessed with a component assay consisting of the substrates of fB/C3b and the enzyme fD*

**IC₅₀ FOR INHIBITION OF FACTOR B CLEAVAGE**

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC₅₀ (nM)</th>
<th>SD (nM)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACH-4471</td>
<td>20</td>
<td>7.5</td>
<td>4</td>
</tr>
</tbody>
</table>

*M: Cleaved products are examined by protein gel. Quantity of Bb is determined by ELISA. fB = Factor B

ACH-4471
Potent Inhibition of AP-Mediated Terminal Pathway Activation

- Inhibition of proteolytic activity of factor D results in inhibition of AP-mediated terminal pathway activation

**DOSE-RESPONSE CURVES WITH AP HEMOLYSIS ASSAY**

![Graph showing dose-response curves with AP hemolysis assay](image)

**POTENCY DETERMINATION WITH AP HEMOLYSIS ASSAY**

<table>
<thead>
<tr>
<th>Compound</th>
<th>EC&lt;sub&gt;50&lt;/sub&gt; (SD) in nM</th>
<th>EC&lt;sub&gt;90&lt;/sub&gt; (SD) in nM</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACH-4471</td>
<td>17 (± 11)</td>
<td>70 (± 23)</td>
<td>6</td>
</tr>
</tbody>
</table>

AP, alternative pathway
Source: Data on File. Achillion Pharmaceuticals, Inc. 2015.
ACH-4471
Highly Specific for Inhibition of Factor D

- ACH-4471 (@10 mM concentration) displays minimal inhibition of other human serine proteases
- ACH-4471 displays high selectivity for Factor D (IC50 = 20 nM)

![Graph showing % Inhibition for various proteases with ACH-4471 inhibition levels.

Source: Data on File. Achillion Pharmaceuticals, Inc. 2015.
Cynomolgus monkeys dosed orally with ACHN fD inhibitors
- ACH-4471 (200 mg/kg, Q12H)

Inhibitory effect on AP activity was assessed ex vivo with Wieslab AP ELISA assay

Complete and sustained suppression of AP activity was demonstrated for >24 hours oral dosing

AP, alternative pathway; fD = Factor D
ACH-4471
PK/PD after Oral Dosing in NHP

- Ex-vivo PK/PD analyses with ACH-4471 (N=8) confirmed that an exposure of > 100 ng/mL is sufficient for >90% inhibition of complement AP activity

**ACH-4471 (Fit with Emax Model)**

<table>
<thead>
<tr>
<th>Concentration (ng/mL)</th>
<th>% Inhibition of TCC Formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>100</td>
<td>100%</td>
</tr>
<tr>
<td>200</td>
<td>90%</td>
</tr>
<tr>
<td>300</td>
<td>80%</td>
</tr>
<tr>
<td>400</td>
<td>70%</td>
</tr>
<tr>
<td>500</td>
<td>60%</td>
</tr>
<tr>
<td>600</td>
<td>50%</td>
</tr>
<tr>
<td>700</td>
<td>40%</td>
</tr>
<tr>
<td>800</td>
<td>30%</td>
</tr>
<tr>
<td>900</td>
<td>20%</td>
</tr>
<tr>
<td>1000</td>
<td>10%</td>
</tr>
<tr>
<td>1100</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Best-fit value**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC₅₀</td>
<td>15.84 (± 1.414)</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>13.06 – 18.61</td>
</tr>
</tbody>
</table>

AP, alternative pathway

Source: Morgan BP et al. 56th Annual Meeting of the American Society of Hematology; 2014; abstract 4817.
Data on File. Achillion Pharmaceuticals, Inc. 2015.
ACH-4471
ADME

ABSORPTION
- Highly permeable with low efflux potential.
- Most likely not a substrate for intestinal Pgp and BCRP transporters
- Rapid absorption after PO dosing: Oral bioavailability is 30% - 70%

DISTRIBUTION
- Highly bound to plasma with a free fraction of 5% in human plasma.
- Minimal partitioning into blood cells
- Steady state volume of distribution (Vss) is moderate

METABOLISM
- Low inhibition potential against all major CYP-P450 isozymes
- No time-dependent inhibition of CYP3A4
- Low metabolic turnover in human liver microsomes
- Not an inducer of human P450 enzymes

SAFETY ASSESSMENT
- High safety margins achieved in repeat dose toxicity studies which support clinical development of ACH-4471
PNH: ON ANTI-C5 ANTIBODY

A PNH red cell is protected from intravascular hemolysis but becomes susceptible to extravascular hemolysis.
Limitations of Current C5 –Targeted Therapies

- Intravenous administration
- ~ 25% of PNH patients have suboptimal response
  - Symptomatic extravascular hemolysis due to accumulation of C3 fragments on PNH red cells
  - Mutations that prevent binding of eculizumab to C5

Complement Factor D Inhibitors

PNH: ON FACTOR D INHIBITOR

A PNH red cell will be protected from both intravascular and extravascular hemolysis

Revised from Luzzatto L, Risitano AM, Notaro R. Haematologica 2010;95(4):523–526
ACH-4471

Significantly Reduce C3b/iC3b Deposition on PNH Erythrocytes

**IC\textsubscript{50} = 32 nM**

Brodsky et al. 51\textsuperscript{st} ASH Meeting, Dec. 2015. Data on file, Achillion Pharmaceuticals, Inc.
ACH-4471
Dose-Dependent Reduction of Hemolysis on PNH Erythrocytes

PATIENT 1

PATIENT 2

PATIENT 3

Patent 1 IC₅₀ (nM) IC₉₀ (nM)
ACH-4471 27 110
ACH-3856 17 56

Patent 2 IC₅₀ (nM) IC₉₀ (nM)
ACH-4471 4 14
ACH-3856 3 6

Patent 3 IC₅₀ (nM) IC₉₀ (nM)
ACH-4471 14 26
ACH-3856 10 45

ACH-4471
Program Next Steps

PHASE 1 (FIRST-IN-HUMAN)
- Single and multi-ascending doses in healthy volunteers
- Initial investigation of safety and pharmacokinetics (PK)

PHASE 1B/2A (PROOF OF CONCEPT)
- Lactate dehydrogenase (LDH), a sensitive marker of hemolysis, can be used to establish POC
- Multiple ascending doses (7 – 14 days) in treatment-naïve PNH patients
- Assess safety of multiple doses in PNH patients
- Establish initial PK/PD (pharmacodynamics)
ACH-4471

Summary

- ACH-4471 is an orally bioavailable, potent, and specific complement factor D inhibitor

- *In vitro* and non-clinical safety data indicate potential for good safety & tolerability

- ACH-4471 demonstrates:
  - High affinity binding to Factor D resulting in inhibition of AP-mediated complement pathway activation
  - Effective blocking of C3 fragment deposition on cells, in contrast to C5-targeted therapies
  - Complete suppression of complement AP activity after oral dosing to non-human primates

- ACH-4471 represents a promising oral therapy for PNH and other complement-mediated diseases

AP, alternative pathway; PNH, paroxysmal nocturnal hemoglobinuria