Fighting Diseases of the Complement Alternative Pathway

April 2018
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Achillion: Research Realized

First-in-class pipeline for complement AP-mediated rare diseases

Strong market opportunities for fD inhibitor portfolio

Patient-focused and experienced management team

$331.8M AT YE‘17 to support multiple value infection points
## Complement Factor D Portfolio

### MILESTONES

**Interim data in 2H18**

**Interim data 4Q18**

**Data in 2019**

**Interim 14-day data 3Q18**

**Interim ~3-month data 4Q18**

### PROGRAM | INDICATION

<table>
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<tr>
<th>PROGRAM</th>
<th>INDICATION</th>
<th>DELIVERY</th>
<th>PRECLINICAL</th>
<th>CLINICAL</th>
<th>MILESTONES</th>
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<tr>
<td>ACH-4471</td>
<td>Factor D Inhibitor</td>
<td>Oral</td>
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<td>C3G: 12-month open label</td>
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<td>C3G: 6-month randomized, double-blind trial</td>
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<td>PNH: Monotherapy open-label untreated PNH</td>
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<td>PNH: Add-on to eculizumab sub-optimal PNH responders</td>
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<td>ACH-5228</td>
<td>Next-Generation Factor D Inhibitor</td>
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Mechanism Matters: Factor D Inhibition

**Classical Pathway**
- C1q
- C1r-C1s
- C4
- MBL
- MASP-1,2
- C3
- C3b
- Bb
- C4b2a3b
- C3d
- C3dg
- iC3b
- C5
- C5b
- C5b6-9
- C6
- C6-9
- C7
- C8
- C9

**Terminal Pathway**
- C5b
- C6-9
- C7
- C8
- C9

**Lectin Pathway**
- C1q
- C1r-C1s
- MBL
- MASP-1,2
- C3
- C3b
- Bb
- C4b2a3b
- C3d
- C3dg
- iC3b
- C5
- C5b
- C6
- C6-9
- C7
- C8
- C9

**Alternative Pathway**
- C3
- C3b
- Bb
- C4b2a3b
- C3d
- C3dg
- iC3b
- C5
- C5b
- C6
- C6-9
- C7
- C8
- C9

**FACTOR D**
A critical control point specifically within the AP

**TRIGGER POINT INHIBITOR**
Prevents amplification and modulates downstream complement cascade
C3 Glomerululopathy (C3G)

Rare Kidney Disease Associated with AP Hyperactivity
C3 Glomerulopathy
A Rare Disease with No FDA-Approved Treatment

Significant unmet medical need as nearly half of C3G patients progress to end-stage renal disease

- C3G caused by dysregulation of the complement system, leading to deposition of C3G fragments on the kidney
- 30–50% progress to ESRD within 10 years
- Significant disease burden at onset — inflammation, profound fatigue and weakness
- Greater than 50% of patients experience disease recurrence post renal transplant, with a 50% chance of graft loss

Normal Alternative Pathway and Kidney Histology

NORMAL KIDNEY HISTOLOGY

NORMAL GLOMERULAR FUNCTION
- No Proteinuria
- Normal GFR

NORMAL GLOMERULAR FUNCTION
- No Proteinuria
- Normal GFR

Fluid Phase

C3 protein
Factor D
C3G is a DISEASE of DEPOSITION
Results in abnormal glomerular function
• Proteinuria
• Reduced GFR
C3 Glomerulopathy

Patients Need Effective Treatments that Address Root Cause

- Significant physical and emotional toll on patients including:
  - Hypertension and edema
  - Susceptibility to infection
  - Anxiety and depression from uncertainty regarding progression

- No approved therapies to treat disease and limited therapies to address edema and fatigue

- Urgent need for disease-modifying treatment to maintain kidney function in native or transplanted kidneys
ACH-4471
C3G: Phase 2 Clinical Development Program

Interim Data and Next Steps
C3 Glomerulopathy
Phase 2 14-Day Trial in Patients with C3G

Clinical Trial Design

**Group 1:** 2 patients received ACH-4471 100mg TID x 14 days followed by 7-day taper

**Group 2:** Up to 8 additional patients to receive ACH-4471 200mg TID x 14 days followed by 7-day taper

Criteria

Must have confirmed diagnosis of C3G

C3 must be <50% LLN with C4 >90% LLN

Estimated glomerular filtration rate cannot be < 45 ml/min/1.73m²

Outcome Measures

Changes in biomarkers of alternative pathway activity (AP) including:

- C3 fragments and intact C3 levels, Bb, and Ba
- Proteinuria
- Pharmacokinetic profiles

Clinical Trial Status

✓ Group 1: Complete

○ Group 2: Ongoing
Phase 2 14-day Trial in Patients with C3G

Baseline Characteristics

Patient A: Adult male with C3G; diagnosed in March 2017

Key concomitant medications
- Prednisolone
- Mycophenolate
- Enalapril
- Spironolactone

Disease characteristics at baseline:
- Proteinuria: Albumin to Creatinine ratio (ACR) 259.3 mg/mmol (ref range: 0 – 2.5)
- Fragment: Intact C3 ratio: 0.1692 (ref range: 0.0085 – 0.0949)

Patient B: Adult male with nephrotic syndrome; diagnosed with C3G in November 2016

Key Concomitant medications:
- Irbesartan
- Spironolactone

Disease characteristics at baseline:
- Proteinuria: Albumin to Creatinine ratio (ACR) 580.3 mg/mmol (ref range: 0 – 2.5)
- Fragment: Intact C3 Ratio: 0.1775 (ref range: 0.0085 – 0.0949)
Phase 2 14-day Trial in Patients with C3G

Patient A: Biomarker Improvements

- Improvement in fragment:intact C3 ratio observed during dosing
- Mechanistic approach facilitates ability to address root cause of AP-mediated diseases

Additional biomarkers improvements observed:
- 30% reduction in Bb level as compared to baseline
- Improvement in complement proteins in the kidney
- 4.4-fold improvement in Ba:creatinine ratio over baseline

- Decreased Ba levels, resulting from inhibited cleavage of factor B by factor D
- Lower levels of Ba suggest lower levels of C3 convertase that would result in fewer C3 fragments
Phase 2 14-day Trial in Patients with C3G

Patient A: Significant Reduction in Proteinuria Observed

Time-dependent decrease observed in proteinuria as measured by ACR

Greater than 50% reduction achieved during 14 days of treatment

ACH-4471 demonstrated potential early signs of clinical benefit
Phase 2 14-day Trial in Patients with C3G

Patient B: Biomarker Improvements

- Improvement in fragment:intact C3 ratio observed during dosing
- Mechanistic approach facilitates ability to address root cause of AP-mediated diseases

Additional biomarkers improvements observed:
- 50% reduction in Bb as compared to baseline
- Improvement in complement proteins in the kidney after dosing with ACH-4471
- Observed an 18.6-fold improvement in Ba:creatinine ratio over baseline

**RATIO OF FRAGMENT/INTACT C3**

**EX VIVO Ba FORMATION RELATIVE TO NORMAL HUMAN SERUM**

- Decreased Ba levels, resulting from inhibited cleavage of factor B by factor D
- Lower levels of Ba suggest lower levels of C3 convertase that would result in fewer C3 fragments
**Phase 2 14-day Trial in Patients with C3G**

**Patient B: Significant Reduction in Proteinuria Observed**

**ALBUMIN TO CREATININE RATIO OVER TIME**

- **Dosing**
  - Time-dependent decrease observed in proteinuria as measured by ACR
  - Greater than 50% reduction achieved during 14 days of treatment

- **Taper**
  - ACH-4471 demonstrated potential early signs of clinical benefit

- **Follow up**
C3G Program Accomplishments

**ACH-4471 was safe and well-tolerated**
- No SAEs or AEs of note. Well tolerated both on-treatment and post-cessation.

**Established PoC**
- POC established with 50% improvement in proteinuria
- AP inhibition confirmed based on changes in complement biomarkers

**Regulatory Status**
- Open U.S. FDA INDs for C3G and PNH
- Orphan drug designation for C3G
- Regulatory discussions for Ph 2 design and potential pivotal endpoints

**Ongoing**
- **Phase 2**: Evaluating 200 mg TID ACH-4471 for 14-days – Data 3Q18
- **Phase 2**: 12-month Open Label Trial – Data 4Q18
- **Phase 2**: 6-month Randomized Double-Blind Trial – Data 2019
Pillars of Achillion’s Patient-Focused Support
Moving beyond the Pill

C3G Patient-focused Drug Development
- First PFDD meeting focused on a renal disease led by the NKF and FDA
- Sponsored by Achillion
- Goal was to understand the patient experiences and perspective

WeC3G patient support initiative
- Unites voices of community impacted by disease
- Connects patients and caregivers to each other and to information, support and resources that can shine the light on C3G
- Raises awareness and understanding

Natural history study:
- Ongoing study conducted by Imperial College of London in up to 400 patients globally
- Tracks natural course of disease over 4 years

www.wec3g.com
www.c3gnaturalhistory.org

April 2018
Corporate Overview
Paroxysmal Nocturnal Hemoglobinuria (PNH)

Rare Disease Characterized by Destruction of Red Blood Cells by the AP
PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)
Factor D and Potential Protection from Intra- & Extra-vascular Hemolysis

PNH RBCs treated with a fD inhibitor may be protected from both intra- and extra-vascular hemolysis.

Type III PNH erythrocytes

No treatment

Intra-vascular hemolysis

Anti-C5 therapy

C3 fragment deposition

Breakthrough and Extra-vascular hemolysis
C3 fragment opsonization via RES macrophages (liver, spleen)

Protected Type III PNH erythrocytes

Factor D inhibitor

Adapted from Luzzatto L, Risitano AM, Notaro R. Haematologica 2010;95(4):523–526.
Study Status and Interim Results
Phase 2 Trial of ACH-4471 in Untreated PNH Patients

Three-month Dose Finding

Enrollment: 4 to 12 pts

KEY INCLUSION / EXCLUSION CRITERIA
- PNH clone size $\geq 10\%$
- Anemia (Hgb < 12 g/dL)
- LDH $\geq 1.5X$ ULN
- ANC $\geq 1,000/\text{mm}^3$
- Platelets $\geq 50,000\, \mu\text{L}$
- Normal ALT
- Alk Phos $\leq 1.5X$ ULN

Objectives
- Reduction in LDH from baseline
- Improvements in Hgb, FACIT
- Increase PNH RBC clone size

PATIENT C
Classic PNH
Total days on therapy: 41
Patient withdrew consent.

PATIENT D
Classic PNH
Total days on therapy: 227

PATIENT B
Aplastic Anemia / PNH
Total days on therapy: 344

PATIENT A
Classic PNH
Total days on therapy: 349

Long-term Extension

Investigator determines clinical response to guide entry into Part 2
Investigator assessment of benefit determines entry into extension trial

Initial dose 100 mg TID. Protocol subsequently amended to allow:
- Newly enrolled patients to start at 150 mg TID
- Intra-patient dose escalation throughout both studies

Patient status as of March 13, 2018

Hgb: hemoglobin | LDH: lactose dehydrogenase| ANC: absolute neutrophil count | ALT: alanine aminotransferase | TID: three times daily
Clinical data generated to date highlight the potential role of factor D inhibition in PNH.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Lactose dehydrogenase (LDH)</td>
<td>Clinically meaningful reduction in LDH</td>
</tr>
<tr>
<td>Hemoglobin (Hgb)</td>
<td>Stabilize / increase hemoglobin</td>
</tr>
<tr>
<td>C3 fragment deposition</td>
<td>Observe no C3 fragment deposition on PNH RBCs</td>
</tr>
<tr>
<td>Fatigue (FACIT scale)</td>
<td>Improvement over time in objective measures of patient fatigue</td>
</tr>
<tr>
<td>PNH RBC Clone Size</td>
<td>Increase percentage of PNH RBC clones from baseline</td>
</tr>
<tr>
<td>Safety</td>
<td>Favorable tolerability profile</td>
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</tbody>
</table>
Phase 2 Trial of ACH-4471 with eculizumab in PNH Sub-optimal Responders

Clinical Trial Design
Open-label study of ACH-4471 with eculizumab

Duration: Six-months of combination treatment

Criteria
Confirmed diagnosis of PNH and on stable dose of eculizumab
Persistent anemia and continued transfusion requirements

Outcome Measures
Change in hemoglobin compared to baseline
Number of units of RBCs during treatment period
Change in LDH compared to baseline

Clinical Trial Status
- Enrollment beginning 1H18
- Interim data anticipated 4Q18
Next-Generation fD Inhibitors

An Expanding Portfolio of Candidates for Complement-mediated Diseases
FACTOR D INHIBITOR PORTFOLIO
ACH-5228 and ACH-5548: Next-Generation Oral Factor D Inhibitors

- Advancing additional fD inhibitors in the clinic
- Creating strategic options for value creation
- Structural alterations achieve significant improvements in potency and pharmacokinetic properties

**ACH-5228**
Phase I single-ascending dose HV study initiated in December 2017

**ACH-5548**
Phase I single-ascending dose HV study targeted for initiation 2Q 2018

Leveraging our unique and deep understanding of the complement system to advance novel, next-generation therapies
Achillion: Research Realized

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