Paroxysmal Nocturnal Haemoglobinuria (PNH) Overview

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Paroxysmal Nocturnal Haemoglobinuria

- Mutation in PIG-A gene
- Loss of GPI-anchored proteins

CD14  CD16  CD24  CD48
CD52  CD55  CD58  CD59
CD66  CD87  CD90  CD109
CD157  CD160

Pathophysiology

Mutation of *PIG-A*

Step 1

GPI-deficient cell

Haematopoietic Stem Cells

Immunological Attack

Step 2

Clonal expansion by immuno-selection

Further clonal expansion

Complement Attack

RBC → Haemolysis

Monocytes

PMN

Platelets

Lymphocytes

Clonal expansion by immuno-selection
PNH is a Progressive Disease of Unregulated Complement Activity

Normal red blood cells are protected from complement attack by a shield of terminal complement inhibitors. Without this protective complement inhibitor shield, PNH red blood cells are destroyed.

Complement Activation

Intact RBC

Haemoglobin released from destroyed PNH RBCs

Anaemia

Thrombosis

Renal Failure

Pulmonary Hypertension

Abdominal Pain

Dyspnoea

Fatigue

Dysphagia

Haemoglobinuria

Erectile Dysfunction

Significant Impact on Survival

Significant Impact on Morbidity

A Hill, Leeds
Under-recognized complications in patients with paroxysmal nocturnal haemoglobinuria: raised pulmonary pressure and reduced right ventricular function

A. Hill et al

Table II. MRI findings in ten patients with paroxysmal nocturnal haemoglobinuria (bold numbers in bottom row are median values).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Disease duration (years)</th>
<th>PNH neutrophil clone size (%)</th>
<th>LDH (u/l)*</th>
<th>Transfused</th>
<th>Primary warfarin</th>
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MRI, magnetic resonance imaging; PNH, paroxysmal nocturnal haemoglobinuria.
*LDH, lactate dehydrogenase: normal range; 160–430 u/l.
†RVEF, right ventricular ejection fraction: normal range; 48–63%.

High Definition Contrast-Enhanced MR Imaging in Paroxysmal Nocturnal Haemoglobinuria (PNH) Suggests a High Frequency of Subclinical Thrombosis
Mortality with supportive therapies only

Supportive therapies, N= 30

Historical Management of PNH

These palliative options do not prevent progression and risk of severe morbidities and mortality

- **Transfusions**
  - Transient treatment of anaemia
  - Iron overload?

- **Anticoagulants**
  - Risk of haemorrhage
  - Non-optimal in many patients*

- **Red cell supplements**
  - Epo may expand clones and increase haemolysis
  - Folic acid, iron

- **Steroids/androgen hormones**
  - Effective when hypoplasia is main concern (not haemolytic PNH)

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Historical Management of PNH (contd)

Allogeneic Bone Marrow Transplantation

- Many PNH patients undergoing BMT have haemolysis and clinical TE - both potential risk factors for poor BMT outcomes.
- Overall survival for unselected PNH patients undergoing allogeneic SCT = 50% to 60% (1, 2).
- Up to 44% mortality at 2 yrs with HLA-matched sibling donor (2, 3).
- Acute GVHD in 34%; chronic GVHD in 33% (2, 3).
- GVHD-free survival in 14% of patients (4).
- When complement inhibition therapies are available BMT should be reserved for patients with severe bone marrow failure.

References:
Impact of Complement

Classical Pathway

Lectin Pathway

Alternative Pathway/Amplification Loop

C1qrs C4a C4d

C4 + C2

C4b2a

C3

C3b

C3bBb

C3bi CR3

C5

C5a

C5b-9 Terminal Complement Complex

C5b C6 C7 C8 C9

Cell Lysis

Cell activation

Proinflammatory

Prothrombotic

Microbial Opsonisation

Immune Complex Clearance

Weak Anaphylatoxin

Potent Anaphylatoxin

Chemotaxis

Cell Activation

Proinflammatory

Prothrombotic

Antibody
Impact of Complement

**Classical Pathway**

- C1qrs
- C4a
- C2b
- C4d

**Lectin Pathway**

- C4b2a
- C3
- C3bi
- C3a
- C3b
- C5

**Alternative Pathway/Amplification Loop**

- C3b or C3(H2O)
- D + B
- Ba

**Proximal**

- Antibody
- C4 + C2
- Factor I
- CD55
- MCP
- CD55
- Factor H
- CD55

**Terminal**

- C5a
- C5b
- C6
- C7
- C8
- C9
- CD59

**Weak Anaphylatoxin**

-影响 complement

**Potent Anaphylatoxin**

- Chemotaxis
- Cell Activation
- Proinflammatory
- Prothrombotic

**Microbial Opsonisation**

- Immune Complex
- Clearance

**Cell Lysis**

- Cell activation
- Proinflammatory
- Prothrombotic
Consequence of Complement Dysregulation

Proximal

Weak Anaphylatoxin

C3a

C3

Factor H

C3bi

CR3

Microbial Opsonisation
Immune Complex Clearance

Terminal

PNH

- Haemolysis
- Inflammation
- Platelet Activation
- Platelet Consumption
- Thrombosis
- Kidney Disease
- Vasoconstriction
- Poor QoL
- Mortality

C5

C5a

C5b

CD55

C6

C7

C8

C9

CD59

C3b

C5b-9 Terminal Complement Complex

A Hill, Leeds
Eculizumab Blocks Terminal Complement Activation

- Eculizumab binds with high affinity to C5
- Terminal complement activity is blocked
- Proximal functions of complement remain intact

Weak Anaphylatoxin

Microbial Opsonisation Immune Complex Clearance

C3

C3a

C3b

C3bi → CR3
Reduction in LDH During Eculizumab Treatment

TRIUMPH – Placebo/ Extension
TRIUMPH – Ecu/ Extension
SHEPHERD - Eculizumab

TRIUMPH placebo patients switched to eculizumab after week 26
All TRIUMPH patients entered the long-term extension study

P < 0.001 at all measured timepoints

Median Transfusion Requirements in the 12 months prior to Eculizumab and most recent 12 Months on Eculizumab

66% transfusion independent

A Hill, Leeds
Eculizumab PK/PD in Pilot Study

Pharmacokinetics
Eculizumab dose

Pharmacodynamics
Eculizumab dose

Eculizumab Levels (mg/ml)

Serum Hemolytic Activity (% Lysis)

Time (weeks)

Time (weeks)
Age at start of eculizumab

A Hill, Leeds data, Dec 2014

n = 179
Survival of PNH Patients Treated with Eculizumab Compared with a Matched Normal Population


†Indications for transplantation were recurrent haemolytic crisis, aplastic anaemia and thromboembolism
Summary

- PNH is a complement mediated disorder
- Arises on a background of a bone marrow failure
- Considerable morbidity and mortality due to chronic complement activation
- Eculizumab has shown the effectiveness of terminal complement inhibition in this disorder
- Significantly improved survival and quality of life
- Strategies to consider for future products:
  - Administration route
  - Frequency of administration
  - Prevention of breakthrough haemolysis
  - Cost of therapy
Thank you

PNH National Service
ALN-CC5 for Complement-Mediated Diseases

Pushkal Garg, M.D.
SVP, Clinical Development
Wide range of complement-mediated diseases

- Excessive complement activity drives disease pathophysiology in many indications
  - Paroxysmal nocturnal hemoglobinuria (PNH)
  - Atypical hemolytic uremic syndrome (aHUS)
  - Neuromyelitis optica (NMO)
  - Myasthenia gravis (MG)
  - Many others

- Soliris™ (eculizumab) is blockbuster drug
  - >$1.5B in reported 2013 sales
  - >$2.1B in reported 2014 sales
Current PNH Treatment Challenges
Breakthrough Hemolysis & C5 Fluctuations

• Eculizumab is potent inhibitor of C5, however a significant proportion of PNH patients experience breakthrough or occult hemolysis\(^1\)

• Complement C5 is an acute phase protein and inflammation causes C5 fluctuations of up to ~100%\(^2\)

Unmet need exists for new therapeutic options
• Consistent level of efficacy
• SC delivery for more tolerable treatment regimen
• Reduced access barriers

\(^1\)Blood. 2015 Jan 29;125(5):775-83
\(^2\)Data illustration adapted from Int Archs Allergy appl Immun 48: 706-720 (1975)
## ALN-CC5 for Complement-Mediated Disease
### Alnylam Reproducible and Modular Platform

<p>| | | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>1</strong></td>
<td><strong>Genetically validated, liver-expressed target gene</strong></td>
<td><strong>Complement C5</strong> is key component of terminal complement pathway; clinically validated in PNH &amp; aHUS</td>
</tr>
</tbody>
</table>
| **2** | **Biomarker for POC in Phase 1** | Blood-based biomarkers associated with complement activity:  
  - C5  
  - Serum hemolytic activity  
  - Lactate dehydrogenase (LDH) |
| **3** | **Definable path to approval and market** | Small pivotal study in PNH patients  
Established endpoints:  
  - LDH reduction  
  - Transfusions |
ALN-CC5 Phase 1/2 Study Design
Healthy Volunteers and Patients with PNH

Part A: Single-Ascending Dose (SAD): Healthy Volunteers
Randomized 3:1, double blind, placebo controlled, N=4

- 50 mg x 1 SC
- 200 mg x 1 SC
- 400 mg x 1 SC
- 600 mg x 1 SC
- 900 mg x 1 SC

Part B: Multiple-Ascending Dose (MAD): Healthy Volunteers
Randomized 3:1, double blind, placebo controlled, N=4

- 100 mg qW x 5 SC
- 200 mg qW x 5 SC
- 400 mg qW x 5 SC

Part C: Multiple Dose (MD): Patients with PNH
Open label, N ~ 16

ALN-CC5 dosed subcutaneously, 200 mg/mL
Initial ALN-CC5 Phase 1 Study Results
Safety and Tolerability – SAD & MAD

No SAEs and no discontinuations due to AEs

Total of 29 AEs reported in SAD phase
• All reported AEs mild or moderate in severity
• Most common (≥10%) AEs: headache, influenza-like illness, nasopharyngitis, nausea, injection site pain, seasonal allergy
• 3 AEs possibly related to treatment
  ◦ nasopharyngitis, injection site pain, injection site rash‡
• ISRs seen in 2 subjects - all mild and transient

Total of 30 AEs reported in MAD phase
• All reported AEs mild or moderate in severity
• Most common (≥10%) AEs: headache, nasopharyngitis, vulvovaginal candidiasis
• 12 AEs possibly related to treatment
  ◦ headache, bruise, cold symptoms, injection site edema, vaginal thrush, redness at injection site, itching at injection site, mouth ulcer
• ISR seen in 4 subjects – all mild and transient

No clinically significant changes in vital signs, EKG, physical exams or clinical laboratories

Safety results currently blinded to treatment with ALN-CC5 or Placebo

*Data as of 10/19/2015
‡ Currently coded in database as rash
ALN-CC5 Phase 1/2: Part A (SAD)
Pharmacodynamics and Clinical Activity: Serum C5

**Serum C5 knockdown following single dose of ALN-CC5**

- Maximum C5 knockdown relative to baseline up to 99%
- Mean maximum C5 knockdown of 98 ± 0.9% (mean ± SEM)
- Mean C5 knockdown of 96 ± 1.0% (mean ± SEM) at Day 98 (900 mg)

* Data as of 10/19/2015
Serum C5 knockdown following 5 weekly doses of ALN-CC5

- Maximum C5 knockdown relative to baseline up to 99%
- Mean maximum C5 knockdown of $98 \pm 0.5$ (mean ± SEM)
- Mean C5 knockdown of $98 \pm 0.3\%$ (mean ± SEM) at Day 112 (5 x qw, 200 mg)

* Data as of 10/19/2015
**Ex Vivo Hemolysis and LDH Results with Eculizumab**

**Chicken RBC hemolysis assay in PNH patients**
- 80-99% inhibition with significant variability

**Sheep RBC hemolysis assay in aHUS patients**
- 40-90% inhibition with significant variability

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Phase 1/2 Study Includes Multiple Assays to Assess for Clinically-Relevant Complement Inhibition

<table>
<thead>
<tr>
<th>Assay</th>
<th>Disease</th>
<th>Observed values</th>
<th>Desired Profile for ALN-CC5</th>
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<tbody>
<tr>
<td>Free C5 (Electrohemiluminescence immunoassay)</td>
<td>aHUS (patients treated with eculizumab)</td>
<td>93.5% max % C5 inhibition(^1), i.e. ~6.5 mcg/mL free C5</td>
<td>&lt;6.5 mcg/mL residual C5</td>
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<tr>
<td>CAP/CCP (Wieslab® ELISA assays)</td>
<td>Genetic C5-9 complement deficiency</td>
<td>&lt;10%(^2) compared to normal serum</td>
<td>&lt;10% CAP/CCP activity</td>
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<tr>
<td>Sheep erythrocyte hemolysis assay</td>
<td>aHUS (patients treated with eculizumab)</td>
<td>40-90% inhibition of hemolytic activity(^3)</td>
<td>80% inhibition of hemolytic activity</td>
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</table>

\(^1\)ASCPT Annual Meeting, Atlanta, GA, March 18-22, 2014, Abstract #387
\(^3\)J Thromb Haemost 2014;12(9):1440-8
Eculizumab vs ALN-CC5
Indirect Comparison of Residual C5 and Free C5

**Eculizumab and free C5 levels (μg/mL)**
- Ecu concentration-effect relationship for reduction in free C5 in aHUS patients
- Maximum % inhibition free C5 of 93.5%
- Estimated at mean of ~6.5 mcg/mL

**ALN-CC5 and residual C5 levels (μg/mL)**
- Serum C5 levels after multiple doses of ALN-CC5 in healthy human volunteers
- Maximum % inhibition residual C5 of 99%
- Mean maximum residual C5 of 1.3 mcg/mL

* Residual C5 levels achieved with ALN-CC5 comparable to free C5 levels in patients on Eculizumab

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1 ASCPT Annual Meeting, Atlanta, GA; March 18-22, 2014; Abstract # 387
2 Data as of 10/19/2015; **There are no head-to-head studies comparing eculizumab and ALN-CC5
**ALN-CC5 Phase 1/2: Part B (MAD)**

**Pharmacodynamics and Clinical Activity: Complement Inhibition**

### Complement Alternative Pathway inhibition (CAP C5b-9 ELISA)

- 5 weekly doses of ALN-CC5
- Maximum CAP inhibition up to 97%
- Mean maximum CAP inhibition of 95 ± 1.0% (mean ± SEM)
- CAP activity comparable to homozygous C5 deficient subjects\(^1\) in MAD 200 & 400 mg

### Complement Classical Pathway inhibition (CCP C5b-9 ELISA)

- 5 weekly doses of ALN-CC5
- Maximum CCP inhibition up to 97%
- Mean maximum CCP inhibition of 96 ± 0.9% (mean ± SEM)
- CCP activity comparable to homozygous C5 deficient subjects\(^1\) in MAD 200 & 400 mg

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Data as of 11/6/2015
**ALN-CC5 Phase 1/2: Part B (MAD)**

**Pharmacodynamics and Clinical Activity: Hemolysis Inhibition**

**Inhibition of sheep erythrocyte hemolysis**

- 5 weekly doses of ALN-CC5
- Maximum serum hemolysis inhibition relative to baseline up to 98%
- Mean maximum serum hemolysis inhibition of $84 \pm 7.6\%$ (mean $\pm$ SEM)

![Graph showing hemolysis inhibition over time](image-url)

*X Data as of 10/19/2015*
**ALN-CC5 Phase 1/2: Part B (MAD)**
Summary of Preliminary Results

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<td><strong>Part B: Multiple Ascending Dose (MAD)</strong></td>
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<td>Weekly (\times 5) subcutaneous injections</td>
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<td><strong>C5 knockdown</strong></td>
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<td>Mean max; % ± SEM</td>
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<td>Max; %</td>
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<td><strong>Residual C5 levels</strong></td>
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<td>Mean nadir; mcg/mL ± SEM</td>
<td>67.5 ± 2.1</td>
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<td>Nadir; mcg/mL</td>
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<td><strong>CAP inhibition</strong></td>
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<td>Mean max; % ± SEM</td>
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<td>Max; %</td>
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<td><strong>CCP inhibition</strong></td>
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<td>Mean max; % ± SEM</td>
<td>18 ± 7.5</td>
<td>85 ± 2.6</td>
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<td>Max; %</td>
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<td><strong>Hemolysis inhibition</strong></td>
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<tr>
<td>Mean max; % ± SEM</td>
<td>5 ± 2.9</td>
<td>52 ± 4.9</td>
<td>75 ± 8.0</td>
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<tr>
<td>Max; %</td>
<td>10</td>
<td>58</td>
<td>91</td>
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</table>

* C5 data as of 10/19/2015; CAP/CCP data as of 11/6/2015; hemolysis data as of 10/5/2015
ALN-CC5 Phase 1/2 Study
Part C in PNH Patients Initiating Shortly

**Study Design**
- Open-label MD study in PNH patients (N~16)

**Primary Objective**
- Safety and tolerability of multi-dose in PNH patients

**Secondary Objectives**
- PK/PD and clinical activity
  - C5 levels, hemolysis suppression
  - LDH reduction

**Note** - Circles represent targeted results for Part C of study

99% C5 Knockdown
~1 mcg/mL
CAP/CCP inhibition as in HoC5 Deficiency
Sheep RBC Hemolytic Activity at 80%

LDH Data in Mid-2016
ALN-CC5 Product Opportunity

Significant potential for a C5 synthesis inhibitor

- Differentiated approach with potential to clamp down C5 levels
- Potential to avoid breakthrough hemolysis
- Subcutaneous, once-monthly to once-quarterly dosing would offer convenient treatment option
- Opportunity to improve access to therapy
  - >5,000 patients with PNH & aHUS on eculizumab; an even greater number in major markets not on treatment
  - Significant restrictions on access to eculizumab in many countries, due to cost burden of treatment
- Initial focus on PNH with plan to expand to other indications, such as aHUS
ALN-CC5 Potential in Wide Range of Complement-Mediated Diseases

Epidemiology: Low: >50:1M; Medium: 5-50:1M; High: <5:1M
Market Development: Composite score of # of agents approved and in company-sponsored development

High
Medium
Low

Inflammatory Myopathies
Membranous Nephropathy
MPGN
Guillain-Barré
Other TMA
Other Genetic Complement Dysregulation

Low
Medium
High

Cardiovascular Disease
Psoriasis
Dry AMD
Rheumatoid Arthritis
Anti-Phospholipid Syndrome
IgA Nephropathy
Lupus Nephritis
Other Neurological Diseases
Myasthenia Gravis
Neuromyelitis Optica
Paroxysmal Nocturnal Hemoglobinuria
Antibody-mediated Rejection

ANCA Vasculitis
Atypical HUS

Other Autoimmune Hemolytic Anemia
Other TMA
Other Genetic Complement Dysregulation
# ALN-CC5 Target Product Profile
## Initial PNH Indication

<table>
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<th>ALN-CC5</th>
<th>Target Product Profile</th>
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<tr>
<td><strong>Indication</strong></td>
<td>Treatment of patients with paroxysmal nocturnal hemoglobinuria to reduce hemolysis</td>
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<tr>
<td><strong>Dose and Regimen</strong></td>
<td>&lt;400 mg, once monthly (qM); possibly once quarterly (qQ)</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>Subcutaneous injection via auto-injector</td>
</tr>
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</table>
| **Efficacy** | Primary Endpoints:  
• Reduction in LDH  
Secondary Endpoints:  
• Reduction in transfusion requirement & transfusion avoidance  
• Hemoglobin stabilization  
• Reduction in thromboembolic events  
• Improvements in fatigue & HR-QoL |
| **Safety** | Comparable or better than MAbs |

Target product profiles for investigational RNAi therapeutics reflect current thinking on desired product characteristics and are subject to change.
Potential Phase 3 Study Designs for ALN-CC5 in PNH*

**STUDY 1†**

**Population:**
- Adults with PNH clone
- LDH > 1.5 x ULN
- Hx of transfusion
- Eculizumab-naïve
- N~40

2:1 RANDOMIZATION

ALN-CC5‡

OR

Placebo‡

**Endpoints (at 6 months):**
- LDH
- PNH symptoms
- Transfusion requirements

‡Early escape to active therapy for non-responders

**STUDY 2†**

**Population:**
- Adults with PNH clone
- On stable eculizumab (+/- inadequate response)
- N~60

ALN-CC5

**Endpoints (at 6 months):**
- LDH
- PNH symptoms
- Transfusion requirements

*Preliminary plans subject to further diligence and health authority feedback
†Patients in both Study 1 & 2 will be allowed to roll over into open-label extension
ALN-CC5 Program Summary & Next Steps

ALN-CC5 is promising investigational approach for treatment of PNH and other complement-mediated diseases

- Potential to provide consistent level of efficacy by blocking C5 production
- Phase 1/2 study in healthy volunteers & PNH patients ongoing
  - Single- & multiple-dose SC administration generally well-tolerated to date
  - Robust, dose-dependent, and durable KD of serum C5 resulting in low residual levels – at or below levels of free C5 estimated with monoclonal antibody -- supportive of qM or possibly qQ subcutaneous dose regimen.
  - Part C in PNH patients initiating by YE 2015
- Broad development plan to maximize product opportunity
  - Initial development in PNH
  - Parallel development in additional indications
  - Infrequent, SC route of administration and consistent C5 knockdown creates differentiated profile

Next Steps

- Initiate dosing in Part C in PNH patients expected by end of 2015
- Initial data from Part C in PNH patients expected by mid 2016
- Data update from Part C in PNH patients expected by late 2016
- Phase 3 start planned in 2017