ACTELION’S SPECIALTY IMMUNOLOGY PORTFOLIO

Investor Presentation
April 2015
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BUILDING AN ADDITIONAL SPECIALTY FRANCHISE

Jean-Paul Clozel, CEO
STRATEGY FOR VALUE CREATION

SUSTAIN AND GROW THE PAH FRANCHISE

BUILD ADDITIONAL SPECIALTY FRANCHISES

OPTIMIZE PROFITABILITY
WHY NOW?

THOROUGH UNDERSTANDING OF ASSETS

- Optimal trial design – with a clear focus on the patient
- Following discussion with Health Authorities
- Thorough understanding of dose and titration scheme
- Availability of oral active comparator – which can be blinded in RTC
- Financially feasible without compromising profitability
ADVANCING OUR IMMUNOLOGY PORTFOLIO

Guy Braunstein, Head of Global Clinical Development
OVERVIEW

Ponesimod

- Strong Phase II data in multiple sclerosis
- What we did since the completion of Phase II
- New study: OPTIMUM
- Additional program in graft vs. host disease

Actelion’s second S1P₁ receptor modulator

- Phase II study in systemic lupus erythematosus
KEY PROPERTIES

- Profile suitable for once-daily oral dosing
- Selective S1P₁ receptor modulator
- Prevents lymphocytes from leaving lymph nodes
- Lymphocyte reduction is rapid and dose-dependent
- Lymphocyte reduction is rapidly reversible upon discontinuation
- Potential in multiple immunological diseases
STRONG PHASE II DATA IN MULTIPLE SCLEROSIS

PONESIMOD

S1P₁ RECEPTOR IMMUNOMODULATION

Ponesimod is investigational, in development and not approved or marketed in any country.
PHASE II DOSE FINDING STUDY IN MS

STUDY DESIGN

Randomization

Placebo (n=121)
10 mg o.d. ponesimod (n=108)
20 mg o.d. ponesimod (n=116)
40 mg o.d. ponesimod (n=119)

Follow-up

Baseline

Screening Treatment 24 weeks Follow-up

Extension

Core
PRIMARY ENDPOINT: CUMULATIVE NUMBER OF NEW T1 GD+ LESIONS FROM WEEK 12 TO WEEK 24

Per-protocol population

Cumulative new T1 Gd+ lesions from week 12 to week 24 (Mean ± SE)

- Placebo (N=110): 6.2
- Ponesimod 10 mg (N=88): 3.5
- Ponesimod 20 mg (N=98): 1.1
- Ponesimod 40 mg (N=93): 1.4

43% reduction

83% reduction

77% reduction

*p<0.05, ***p<0.0001 vs placebo
SECONDARY ENDPOINT: ANNUALIZED RELAPSE RATE UP TO WEEK 24

All-treated population

- Annualized confirmed relapse rate estimated from negative binomial regression model

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Annualized Relapse Rate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.525</td>
<td>-</td>
</tr>
<tr>
<td>Ponesimod 10 mg</td>
<td>0.332</td>
<td>-</td>
</tr>
<tr>
<td>Ponesimod 20 mg</td>
<td>0.417</td>
<td>-</td>
</tr>
<tr>
<td>Ponesimod 40 mg</td>
<td>0.251</td>
<td>-</td>
</tr>
</tbody>
</table>

52% decrease in annualized relapse rate compared to placebo (p<0.05)
## ADVERSE EVENTS OBSERVED IN ≥5% OF PATIENTS

<table>
<thead>
<tr>
<th>All-treated population</th>
<th>Placebo (n=121)</th>
<th>Ponesimod 10 mg (n=108)</th>
<th>Ponesimod 20 mg (n=114)</th>
<th>Ponesimod 40 mg (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥1 AE</td>
<td>90 (74.4)</td>
<td>83 (76.9)</td>
<td>88 (77.2)</td>
<td>88 (73.9)</td>
</tr>
<tr>
<td>Total number of AEs</td>
<td>310</td>
<td>275</td>
<td>304</td>
<td>325</td>
</tr>
<tr>
<td>Headache</td>
<td>18 (14.9)</td>
<td>15 (13.9)</td>
<td>15 (13.2)</td>
<td>15 (12.6)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>17 (14.0)</td>
<td>16 (14.8)</td>
<td>11 (9.6)</td>
<td>13 (10.9)</td>
</tr>
<tr>
<td>Upper RTI</td>
<td>11 (9.1)</td>
<td>4 (3.7)</td>
<td>9 (7.9)</td>
<td>11 (9.2)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>8 (6.6)</td>
<td>3 (2.8)</td>
<td>3 (2.6)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (5.8)</td>
<td>7 (6.5)</td>
<td>9 (7.9)</td>
<td>6 (5.0)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7 (5.8)</td>
<td>2 (1.9)</td>
<td>1 (0.9)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Back pain</td>
<td>6 (5.0)</td>
<td>2 (1.9)</td>
<td>5 (4.4)</td>
<td>6 (5.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (5.0)</td>
<td>2 (1.9)</td>
<td>3 (2.6)</td>
<td>4 (3.4)</td>
</tr>
<tr>
<td>UTI</td>
<td>6 (5.0)</td>
<td>2 (1.9)</td>
<td>1 (0.9)</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>Oral herpes</td>
<td>6 (5.0)</td>
<td>1 (0.9)</td>
<td>–</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>5 (4.1)</td>
<td>4 (3.7)</td>
<td>5 (4.4)</td>
<td>6 (5.0)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>4 (3.3)</td>
<td>5 (4.6)</td>
<td>7 (6.1)</td>
<td>17 (14.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (2.5)</td>
<td>8 (7.4)</td>
<td>7 (6.1)</td>
<td>11 (9.2)</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>2 (1.7)</td>
<td>2 (1.9)</td>
<td>3 (2.6)</td>
<td>13 (10.9)</td>
</tr>
<tr>
<td>Cough</td>
<td>2 (1.7)</td>
<td>1 (0.9)</td>
<td>3 (2.6)</td>
<td>8 (6.7)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>1 (0.8)</td>
<td>5 (4.6)</td>
<td>7 (6.1)</td>
<td>7 (5.9)</td>
</tr>
</tbody>
</table>

AE, adverse event; ALT, alanine aminotransferase; RTI, respiratory tract infection; UTI, urinary tract infection
OVERALL SAFETY SUMMARY

- No increase in the proportion of patients with infection-associated AEs (placebo 45.5%; ponesimod 10 mg, 37.0%; 20 mg, 32.5%; 40 mg, 36.1%)

- Two malignancies were reported: one case of breast cancer in the ponesimod 10 mg group and one case of cervix carcinoma in the placebo group

- The proportion of patients with respiratory AE was higher in the ponesimod than in the placebo group (placebo, 6.6%; ponesimod 10 mg, 9.3%; ponesimod 20 mg, 16.7%; ponesimod 40 mg, 31.9%)

- No cases of total bilirubin elevation ≥2× ULN and no cases of Hy’s law

- One case of macular edema confirmed by optical coherence tomography resolved after treatment discontinuation
MAXIMUM EFFECT ON LYMPHOCYTES AT 20 MG

All-treated set

Mean change from baseline in lymphocyte count (%)

-80 -70 -60 -50 -40 -30 -20 -10 0 10

Day 8  Day 13  Week 4  Week 8  Week 12  Week 16  Week 20  Week 24

- Ponesimod 40 mg
- Ponesimod 20 mg
- Ponesimod 10 mg
- Placebo
EFFECT ON LYMPHOCYTES IS RAPIDLY REVERSIBLE

Mean change from baseline in lymphocyte count (%)

All-treated set – subset of patient with follow-up visit

- Ponesimod 40 mg
- Ponesimod 20 mg
- Ponesimod 10 mg
- Placebo

Day 8  Day 13  Week 4  Week 8  Week 12  Week 16  Week 20  Week 24 / FU 1  FU 2
WHAT WE DID SINCE COMPLETION OF PHASE II

PONESIMOD

S1P₁ RECEPTOR IMMUNOMODULATION

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WHAT WE DID SINCE COMPLETION OF PHASE II

- Phase II extension ongoing – some treated for more than 5 years
- New titration scheme
- Positive Phase II study in psoriasis – opens door to new indications
- Redesign clinical program
  - based on new therapeutic landscape in multiple sclerosis
  - discussed with regulatory agencies
DOUBLE-BLIND EXTENSION OF THE PHASE II STUDY

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DOUBLE-BLIND PHASE II EXTENSION STUDY DESIGN

Randomization

Placebo

10 mg ponesimod

20 mg ponesimod

40 mg ponesimod

10 mg ponesimod

20 mg ponesimod

40 mg ponesimod

Treatment
24 weeks

Treatment Period 1
Up to 96 weeks

Core

Extension
DOUBLE-BLIND PHASE II EXTENSION STUDY DESIGN

**Treatment**
- **24 weeks**

**Treatment Period 1**
- Up to 96 weeks

**Treatment Period 2**
- Up to 432 weeks

**Randomization**
- Placebo
- 10 mg ponesimod
- 20 mg ponesimod
- 40 mg ponesimod

**Extension Core**
- 10 mg ponesimod
- 20 mg ponesimod
- 10 mg ponesimod
- 20 mg ponesimod

**Follow-up**

**End of Treatment**
EXTENSION STUDY: ARR REDUCTION OVER ~2 YEARS

Annualized Relapse Rates (ARR) (Confirmed Relapses)
Negative Binominal Regressions – All-Randomized Set

RR = 42.3%
p=0.045
V 10mg

RR = 22.5%
p=0.322
V 10mg
EXTENSION STUDY: CURRENT STATUS

- Safety profile consistent with the safety profile from the core study
- Continuing in a blinded fashion with two dose groups – 10 and 20 mg
- More than 4 years of exposure – drop-out rate minimal
- Long-term data with 10 and 20mg will be very useful for registration and launch
- High value of the study due to length, blinded fashion, size, and safety and efficacy endpoints collected at regular intervals
NEW TITRATION SCHEME

PONESIMOD

S1P₁ RECEPTOR
IMMUNOMODULATION

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PHARMACODYNAMIC STUDY

- New titration schemes to mitigate first dose effect
- Simulation work based on PK and PD data used to determine optimal titration scheme
- Confirmed in a specific trial comparing new vs. previous titration scheme
- Results to be presented at the European Association for Clinical Pharmacology and Therapeutics (EACPT) Congress, 27-30 June 2015 in Madrid
PHASE II STUDY IN PSORIASIS

PONESIMOD

S1P1 RECEPTOR IMMUNOMODULATION

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S1P₁ RECEPTOR MODULATORS BEYOND MS

PHASE II STUDY IN PSORIASIS: STATISTICALLY SIGNIFICANT PRIMARY ENDPOINT: PASI75 AT WEEK 16

Patients with missing or invalid assessments were considered as non-responders.

Proportion of patients (%) with ≥PASI75 at Week 16 (± 95% CI)

- Placebo (n=67): 13.4%
- Ponesimod 20 mg (n=126): 46%
- Ponesimod 40 mg (n=133): 48.1%

*p<0.0001 vs placebo
PHASE III OPTIMUM STUDY IN MULTIPLE SCLEROSIS

PONESIMOD

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STUDY OVERVIEW

- OPTIMUM: A Multicenter, randomized, double-blind, parallel-group, active-controlled, superiority study to compare the efficacy and safety of ponesimod to teriflunomide in subjects with relapsing multiple sclerosis

- Pivotal Phase III study
  - ~200 centers in North America, Latin America, Eastern and Western Europe, Pacific (planned)
  - ~1100 patients randomized in 2 groups in a 1:1 ratio to receive either ponesimod 20 mg or teriflunomide 14 mg
  - New titration scheme implemented
  - Enrollment imminent
STUDY OBJECTIVES

Primary objective
- To determine whether ponseimod is more efficacious than teriflunomide in terms of reducing relapses in subjects with relapsing multiple sclerosis

Secondary objectives
- To assess the effect of ponseimod on disability progression and on other aspects of multiple sclerosis disease control;
- To assess the safety and tolerability of ponseimod in subjects with relapsing multiple sclerosis
CHOICE OF ACTIVE CONTROL

- Ponesimod compared to Teriflunomide 14 mg
  - Oral comparator facilitates recruitment and blinding
  - Recently approved first-line therapy for relapsing multiple sclerosis
  - Superiority study possible given incomplete effect of teriflunomide on ARR
  - 14 mg but not 7 mg approved in EU and Australia
OPTIMUM study is enriched with additional endpoints aiming at further differentiation:

- PRO, MRI endpoints, disease activity, prospectively included in protocol
- Compliance enhancement and monitoring tool using electronic device

Additional study in multiple sclerosis to further characterize:

- Clinical utility
- Differentiation
- Discussed with Health Authorities
PHASE II STUDY IN GRAFT VS. HOST DISEASE

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WHY PONESIMOD IN GRAFT VS. HOST DISEASE?

UNMET MEDICAL NEED & SCIENTIFIC RATIONALE

▶ Unmet need
  – Patients with chronic GvHD have a 30-50% mortality during first 5 years of diagnosis
  – Currently no approved therapies for chronic GvHD in US
  – Glucocorticoids (with calcineurin inhibitors) are considered standard treatment
  – Half of patients receiving initial therapy do not have a sustained response

▶ Scientific rationale
  – T and B cells play a key role in pathogenesis
  – S1P₁ receptor modulators have shown efficacy in models of GvHD
PONESIMOD IN GRAFT VS. HOST DISEASE

PHASE II DOSE-ESCALATION STUDY DESIGN

- Open-label, single-arm, intra-subject dose-escalation study to investigate the biological activity, safety, tolerability, & pharmacokinetics of ponesimod in subjects with symptomatic moderate or severe chronic graft vs. host disease inadequately responding to first or second line therapy

- The study will also investigate the clinical response to ponesimod treatment in these patients

- ~ 30 subjects enrolled to receive escalating doses of 5, 10 and 20 mg over the course of 24 weeks

- ~ 10 sites in US expected to last approximately 18 months

- Enrollment imminent
PHASE II STUDY IN SYSTEMIC LUPUS ERYTHEMATOSUS

ACTELION’S 2nd S1P₁ MODULATOR

S₁P₁ RECEPTOR IMMUNOMODULATION

An investigational compound, in development and not approved or marketed in any country.
KEY PROPERTIES

- Very potent S1P₁ receptor modulator with highly selective profile
- Prevents lymphocytes from leaving lymph nodes
- Lymphocyte reduction is rapid, dose-dependent and reversible
- Pharmacokinetic profile suitable for once-daily oral dosing with no need for up-titration regimen
- Potential in multiple autoimmune diseases
WHY $S1P_1$ MODULATOR FOR SYSTEMIC LUPUS ERYTHEMATOSUS?

UNMET MEDICAL NEED & SCIENTIFIC RATIONALE

- Unmet need:
  - Severe organ damage and significant mortality in subset of patients
  - Impaired physical and mental QoL
  - Therapy is largely empirical with use of corticosteroids and other immunosuppressants
  - Only one biologic with limited efficacy gained approval

- Scientific rationale for $S1P_1$ receptor modulation in SLE:
  - T and B cells play a key role in pathogenesis
  - $S1P_1$ receptor modulators have shown efficacy in different preclinical models of SLE: MRL/lpr and BXSB mice
ACTELION’S SECOND S1P₁ RECEPTOR MODULATOR IN SYSTEMIC LUPUS ERYTHEMATOSUS

PHASE II DOSE-ESCALATION STUDY DESIGN

- Prospective, multicenter, multinational, randomized, double-blind, placebo-controlled, dose-response study to investigate the biologic activity, pharmacokinetics, safety, & tolerability of Actelion's second S1P₁ receptor modulator in adult subjects with systemic lupus erythematosus

- ~64 subjects enrolled to receive either 0.5, 1, 2 or 4 mg over the course of 12 weeks

- ~20 sites and expected to last approximately 20 months

- Enrollment imminent
CONCLUSION

- New titration scheme to mitigate first dose effects
- Ponesimod combines selectivity, speed of onset and rapid reversibility
- Long-term safety data
- Multiple sclerosis Phase III study targets superiority over oral active comparator
- Many new features have been included in the Phase III trials
- Building an additional specialty franchise: Additional programs in graft vs. host disease and systemic lupus erythematosus