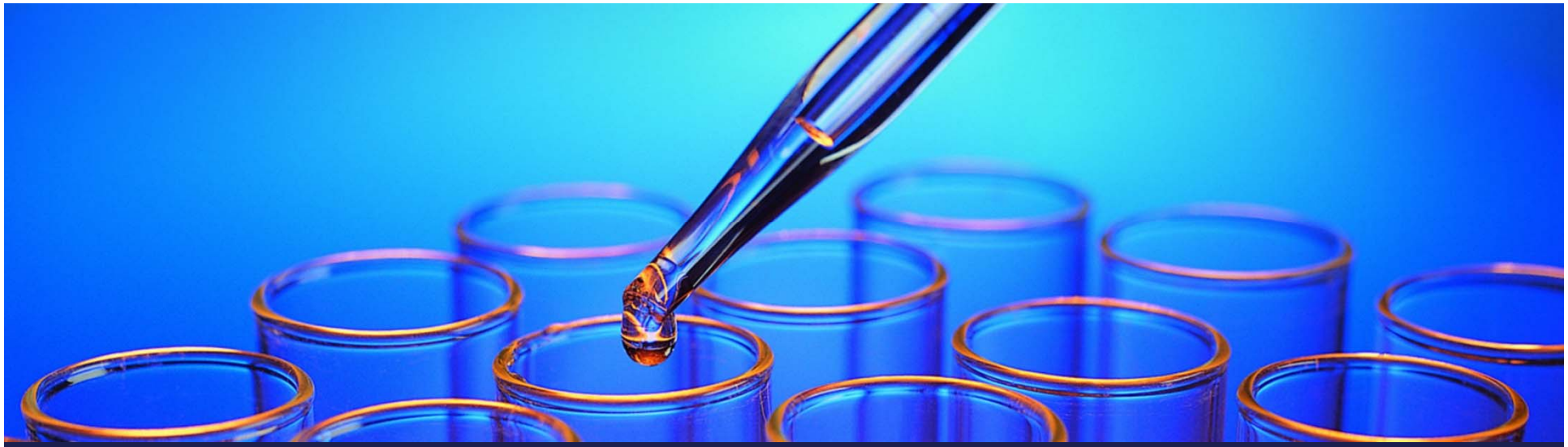

Biopharmaceuticals Investor & Analyst Day

Immunology – from symptom relief to disease modification

Harsukh Parmar
Head of Translational Innovation Platform Immunology

Merck KGaA
Darmstadt · Germany

Darmstadt, Germany – September 18, 2014

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Agenda

Introduction

Systemic lupus erythematosus

Multiple sclerosis and osteoarthritis

Summary

Immunology – The underlying path to many common and rare diseases

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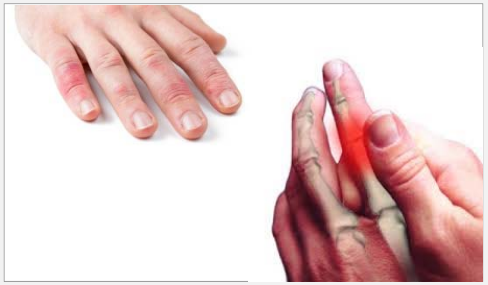
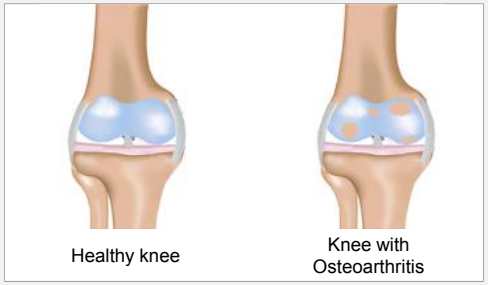
Innovation clusters

Autoimmune & Inflammatory Diseases



- Focus on diseases where we have a good understanding of the biology and patient stratification

Osteoarthritis



- Deliver therapies that grow cartilage, relieve pain and improve function in patients with osteoarthritis

Ambition and objective

- Vision to innovate and deliver 'best in disease' treatments to patients with debilitating or fatal autoimmune diseases
- Focus on innate and adaptive immunity with common pathways shared across a few target indications
- Supporting other therapeutic areas where immunology is a common theme across diverse diseases

Pipeline progress over the last two years

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[1]under preparation for this phase; [2]since Capital Markets Day in May 2012; f.i.m.: first-in-man trial
As of September 2014

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Agenda

Introduction

Systemic lupus erythematosus

Multiple sclerosis and osteoarthritis

Summary

Systemic lupus erythematosus (SLE) represents a major unmet medical need in the area of immunology

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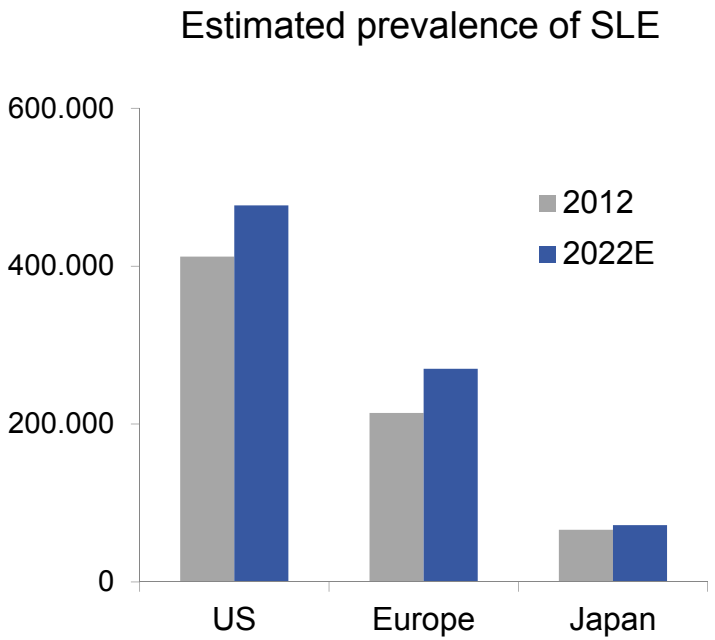
Disease characteristics

- Autoimmune disease which leads to tissue damage across multiple organ systems
- Moderate / severe SLE represents around 50% of cases
- Lupus prevalence varies based on gender and ethnicity
  - 90% female
  - Around three times more common in African-Americans
  - Fairly common in China

SLE market

- Generics dominate the front-line settings (e.g. corticosteroids)
- Lack of approved therapies, high off-label use of immunosuppressives
- Biologics mostly prescribed in the US due to prevalence and budget availability



Source: Decision Resources

Atacicept targets both BLyS and APRIL

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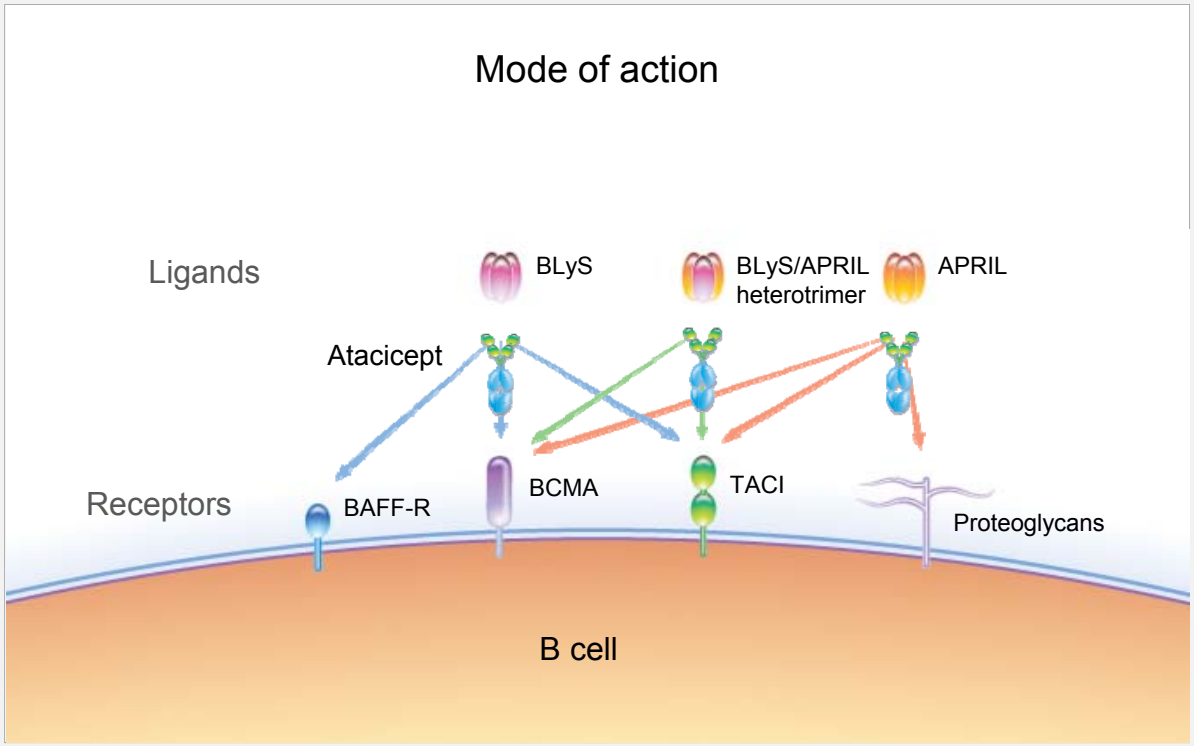

- Atacicept binds to the receptors of two cytokines regulating maturation, function, and survival of B cells
  - B-lymphocyte stimulator (BLyS)
  - A proliferation-inducing ligand (APRIL)
- Also contains extracellular, ligand-binding portion of the receptor TACI
- BLyS and APRIL levels increased in patients with SLE, suggesting dual blockade may be more efficacious than blocking BLyS alone

Source: Dillon S, et al. Arthritis Res Ther. 2010. Dillion SR et al, Nature reviews, Drug Discovery , March 2006

Results of a previous Phase II trial (APRIL-SLE) suggest a potential beneficial effect of atacicept 150 mg

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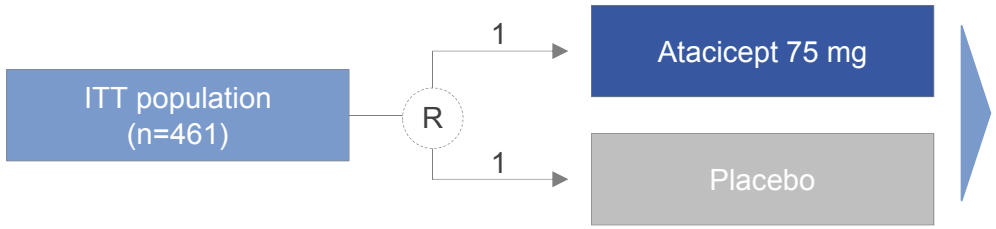
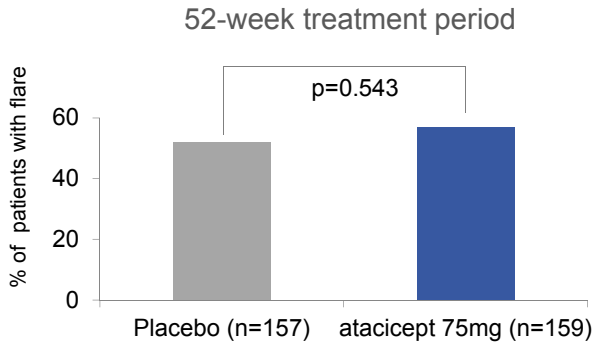
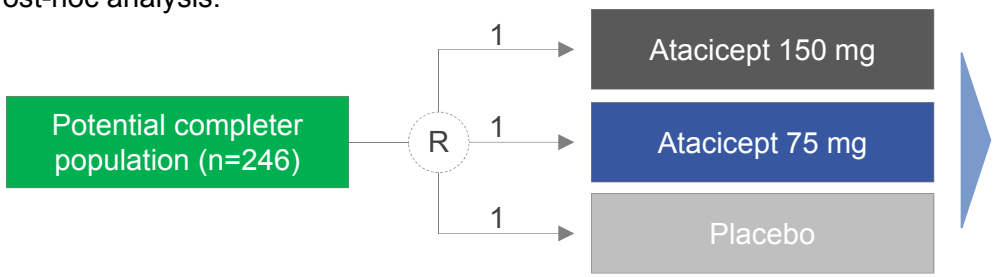
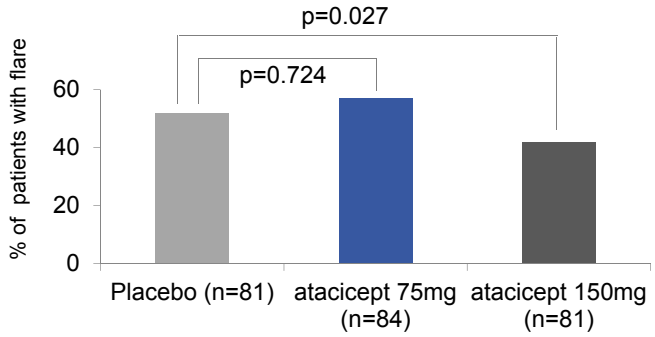
- 52-week, double-blind trial in patients with moderate-to-severe SLE disease
- Primary aim was to prevent new flares
- The atacicept 150 mg arm was discontinued prematurely





Post-hoc analysis:





ITT = intention-to-treat; Potential completer: all subjects who were randomized ≥52 weeks prior to atacicept 150 mg arm termination
Source: Isenberg D. et al, Ann Rheum Dis. 2014

APRIL-SLE efficacy: Significantly longer time to first flare and reduced number of flares in 150 mg group

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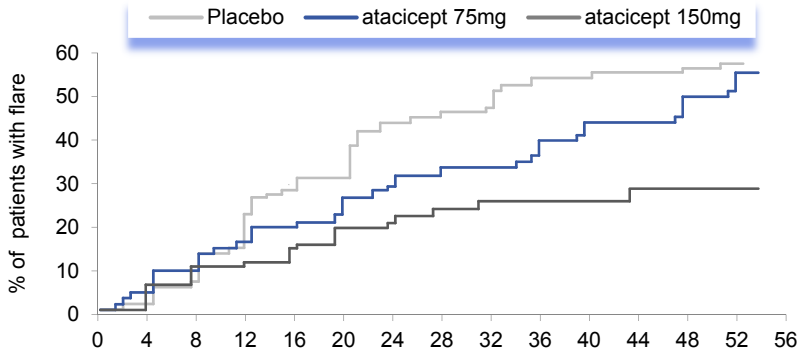
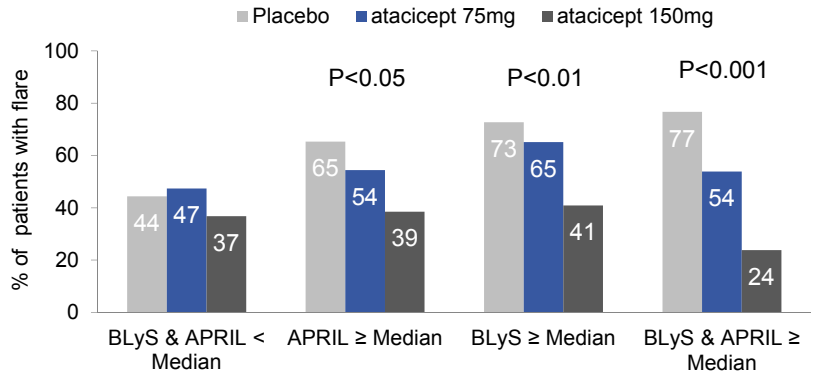


Time to first new flare (BILAG A or B) during treatment, Potential Completer Population



Analysis of potential completer population;
BLyS median = 1.9 ng/mL; APRIL median = 2.24 ng/mL

APRIL-SLE

Post hoc analysis showed that atacicept was associated with a dose-dependent decrease in proportion of patients requiring higher doses of corticosteroids

Treatment group	Any increase in steroid	Increase to ≥20 mg prednisone (high dose)
Placebo	35.6%	32.1%
atacicept 75mg	29.8%	27.4%
atacicept 150mg	13.6%	12.3%

Source: Isenberg D. et al, Ann Rheum Dis. 2014

No increased risk of mild to moderate infection and possibly small increased risk of severe infection

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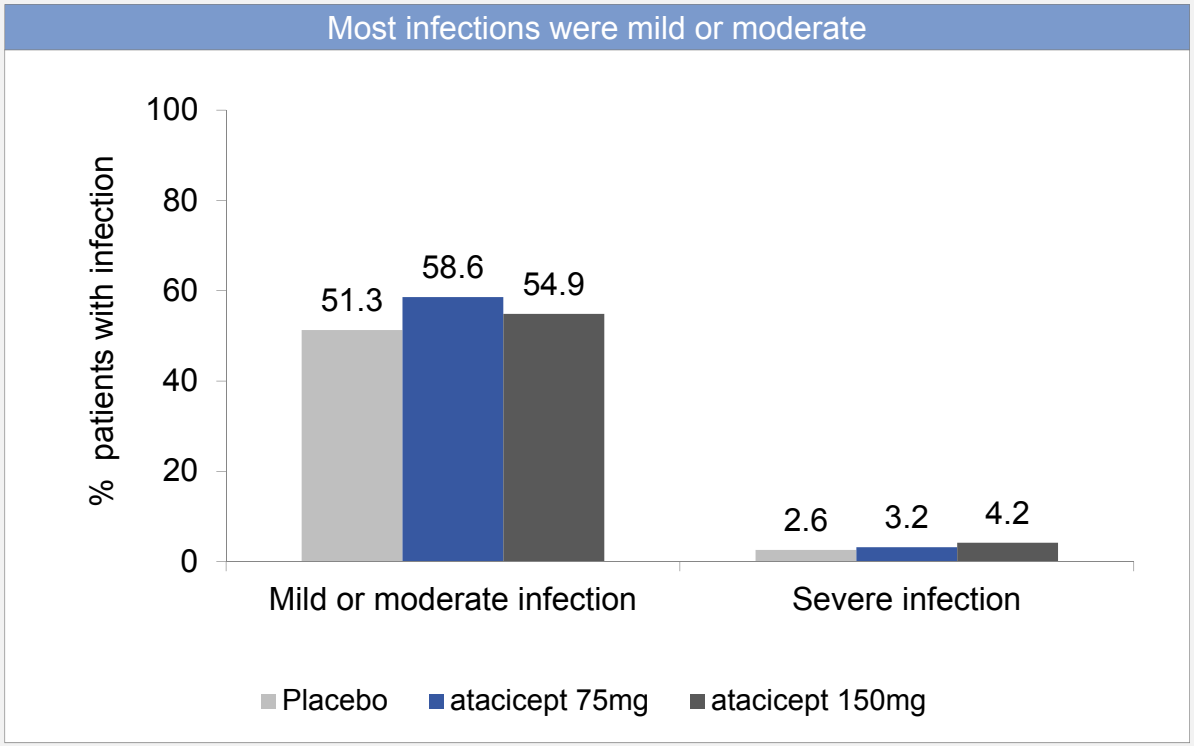

- The safety analysis set consists of 455 patients (all randomized patients who received at least one dose of study medication)
- In neither atacicept arm was the risk of serious infection significantly increased compared with placebo
- Enrollment in the atacicept 150 mg arm was discontinued prematurely due to two deaths from pneumonia complicated by pulmonary hemorrhage
- The infections in these two patients were not associated with hypogammaglobulinemia

Source: Isenberg D. et al, Ann Rheum Dis. 2014

ADDRESS II: Phase IIb of atacicept in SLE patients aiming to show a reduction in disease activity

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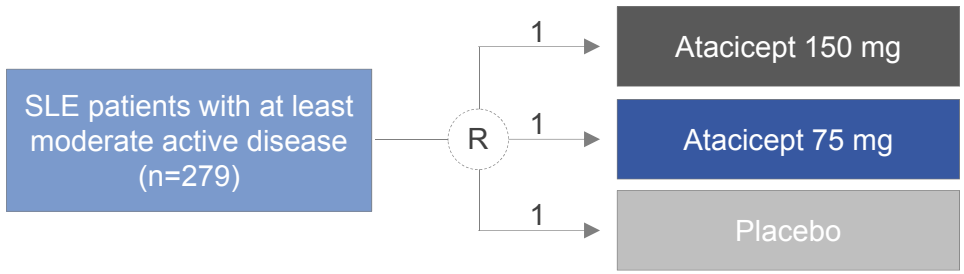
Phase IIb (ADDRESS II) trial design

Atacicept

24-week, randomized, double-blind, placebo-controlled
Subcutaneous injection, once-a-week dosing



Data available in 2016

Study details

- Currently recruiting
- Primary outcome: Percentage of patients with SLE responder index (SRI) response at week 24 compared to screening
- Secondary outcomes include percentage of patients achieving a significant reduction in corticosteroid dose, time to first SRI response and safety
- Two-year Long Term Extension (ADDRESS II LTE) study about to start, to develop safety database

BTK inhibitor: aim to develop a differentiated and selective inhibitor versus competition

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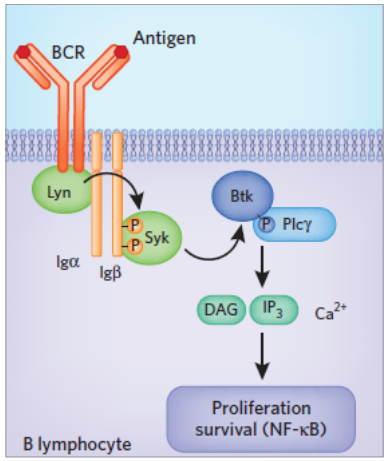
Mode of action

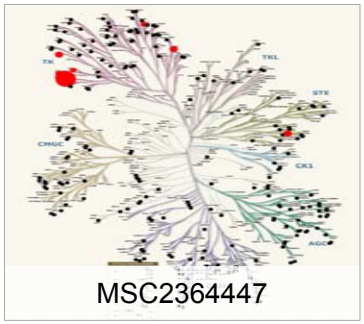
- BTK is expressed by multiple cell types, including B lymphocytes and macrophages
- BTK plays pivotal roles in B cell development, differentiation, activation, class-switching, proliferation, survival, and cytokine release
- In addition, BTK prevents immune complex-mediated signaling and production of inflammatory cytokines in macrophages and glycoprotein VI signaling in platelets

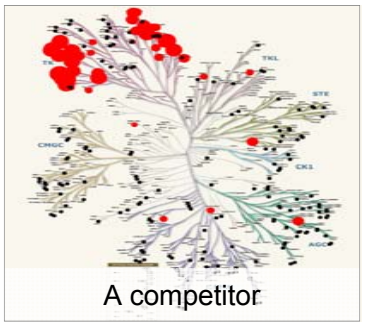
BTK in B lymphocytes



MSC2364447

- Aim to demonstrate greater kinase selectivity profile compared to competitors
- Improved cellular assay target profile for B and T cell interactions
- Aim to achieve best in class through minimization of off-target effects


MSC2364447


A competitor

Picture source: Hendriks, *Nat. Chem. Biology* 2012
BTK = bruton tyrosine kinase

Preclinical development of MSC236447 ongoing

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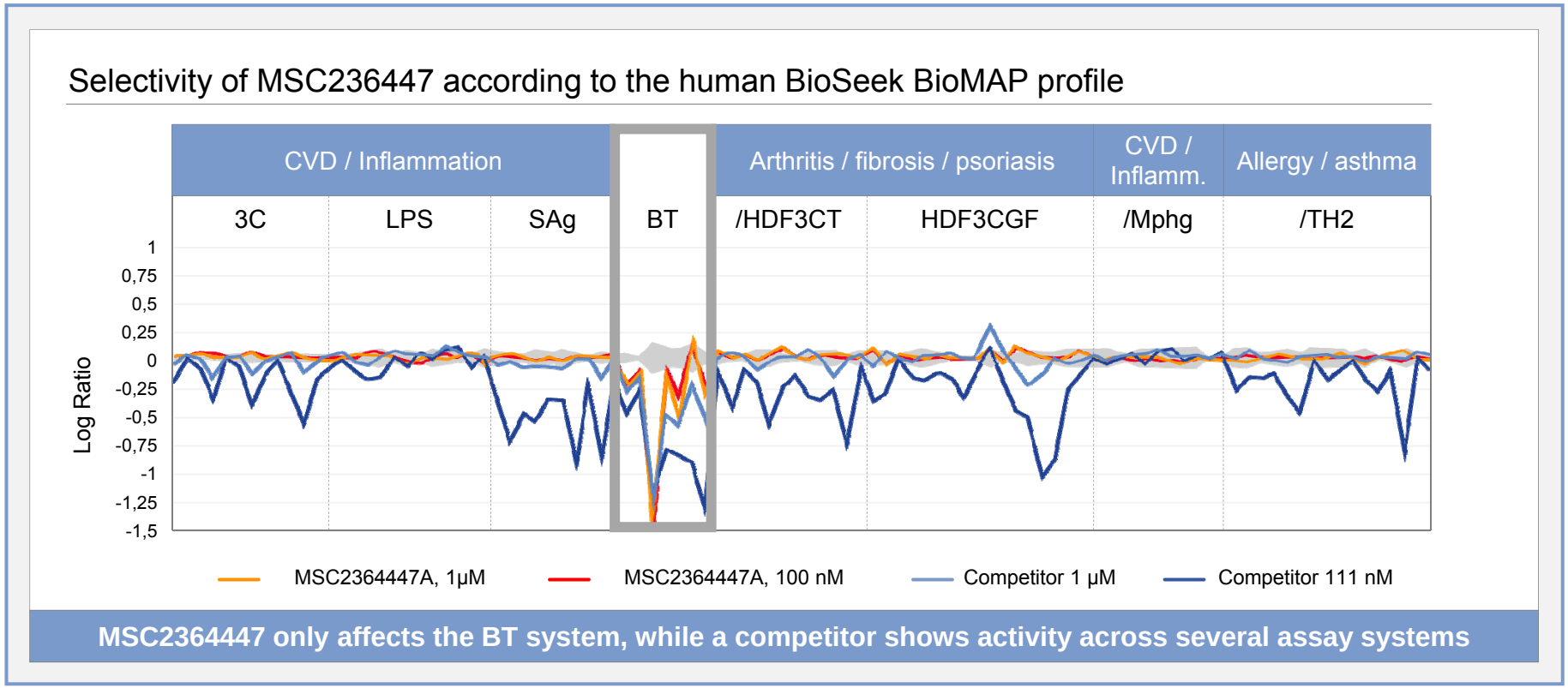

BioMAP: diverse human primary cell-based assays meant to mimic human disease states

BTK inhibition may constitute a promising therapeutic approach for autoimmune disease e.g. RA & SLE

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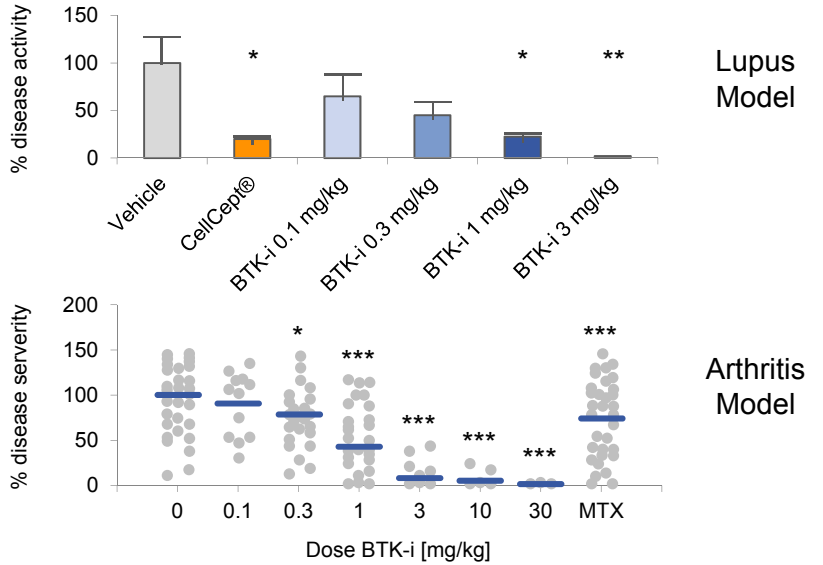
Scientific rationale

- The role of B cells in the pathogenesis of SLE and RA is well-known
- Beneficial effects of BTK-i in mouse models of lupus and RA have been reported in the literature and in our in-house experiments
- BTK-i simultaneously suppress autoantibody-producing cells as well as certain effector cells in RA and SLE

Preclinical results of MSC236447C



Phase I to start in Q4 2014

* = P<0.05; ** = P<0.01; *** = P<0.001
RA = rheumatoid arthritis

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Agenda

Introduction

Systemic lupus erythematosus

Multiple sclerosis and osteoarthritis

Summary

ATX-MS-1467: Scientific rationale

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Compound

- Highly selective immunotolerizing agent that re-balances the immune system while sparing normal immune surveillance
- Four synthetic soluble peptide T-cell epitopes of myelin based proteins (MBP)

Mode of action

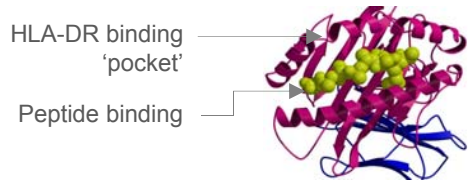
- Designed to bind MS-associated HLA haplotypes (HLA-DR15/DQ6)
- ~30% of Caucasian population estimated to carry the HLA-DR15 allele
- Induces tolerance in MBP-specific pathogenic T cells and facilitates generation of regulatory T cells (Treg)
- Combination of four peptides covers major known MS-associated HLA haplotypes, thus, stratification of patient population is possible

Advantage

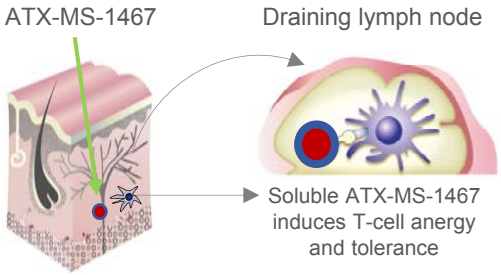
- Potential first-in-class immunotolerizing agent that may extend disease-free state with a favorable safety profile

HLA-DR15/DQ6 haplotype

Dominant haplotype associated with a three-fold increased risk of MS



ATX-MS-1467 injection into the skin



Source: ATX MS 1467 Investigators Brochure, v2, July 2013

ATX-MS-1467: Preliminary MRI data from Phase Ib with ID dosing provides confidence for clinical activity

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Phase Ib study design

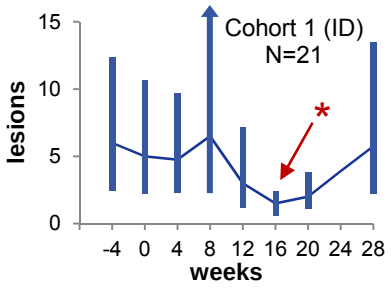
ATX-MS-1467

open label, upward dose titration, two routes of administration
25, 50, 100, 400 followed by 800 ug for 5 doses

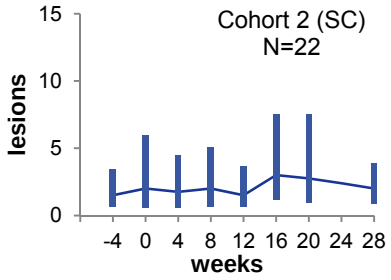
Patients with RRMS (n = 43)

- Intradermal injection (ID) (n = 21)
- Subcutaneous injection (SC) (n = 22)

Phase Ib results



- 9/21 patients had no Gd-enhanced lesions at screening and baseline
- High variability between patients – but individual patients showed same pattern
- Mean number of new Gd lesions measured by MRI is significantly reduced by ATX-1467 treatment



- 13/22 patients had no Gd lesions at screening and baseline
- High variability between patients – but individual patients showed no pattern
- No effect evident

* Week 16 significantly lower than other time points (except week 20)
Repeated Measure Negative Binomial model; LS Means and 95%CI

MRI = magnetic resonance imaging; RRMS = relapsing remitting multiple sclerosis; Gd = gadolinium
Source: Wraith D et al, 15th International Congress of Immunology; Milan, Italy, August 22-27, 2013. Oral presentation S2.03

ATX-MS-1467: Proof-of-principle study involves frequent neuroimaging using MRI

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Phase IIa study design

ATX-MS-1467

multi-center, open-label, single arm, baseline-controlled
4 weeks dose titration period followed by 16 weeks of treatment,
and 16 additional weeks of observation

Patients with RRMS (n=15) → 800µg bi-weekly (following titration) administered intradermally

Currently recruiting, data available in 2016

Details

- Key inclusion criteria: expression of HLA-DR15, evidence of active disease on Gd-enhanced MRI
- Monitoring:
  - MRI pre-, during and post-treatment
  - MBP-specific T-cell reactivity pre- and post-treatment

MRI = magnetic resonance imaging; RRMS = relapsing remitting multiple sclerosis; Gd = gadolinium

Plovamer acetate: Phase II study design aiming for proof-of-confidence in RRMS

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Phase I findings

Single ascending dose study in healthy volunteers[1]

- Safety study. Placebo-controlled, double blind, n=56 (40 PA, 16 placebo)
- Injection site reactions (ISRs) most frequent TEAE (dose dependent), all mild to moderate in severity

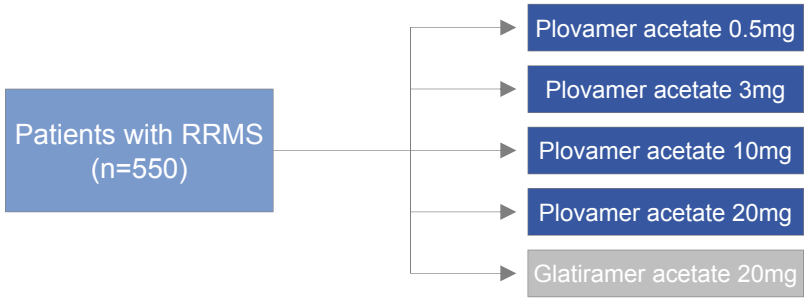
Multiple ascending dose study in patients with secondary progressive MS[2]

- Safety study. Placebo-controlled, double blind for 8 wks, open label for additional 4 wks, n=50 (36 PA for 12 wks, 14 placebo 8 wks, PA 4 wks)
- ISRs most frequent TEAE (dose dependent), all mild to moderate in severity
- Given the observed AEs in the 60 mg dose group, 30 mg considered MTD
- Increased eosinophil count after 60 mg dose treatment (vs. baseline) consistent with an induced Th2 shift
- Trend towards lower MRI lesion number after treatment (low n and baseline differences in dose group limit interpretation of results)

Phase II study design

Plovamer acetate (PA)

randomized, multi-center, parallel-group, rater-blind



- Primary endpoint: Mean no. of gadolinium enhancing T1 lesions from 5 monthly MRIs
  - To be analyzed in biomarker-defined subpopulations
- Secondary endpoints: Mean annualized relapse rate, time to first relapse, % of patients relapse-free
- 130 sites targeted in 17 countries

RRMS = relapsing remitting multiple sclerosis; TEAE = treatment emergent adverse event; MTD = maximum tolerated dose; MRI = magnetic resonance imaging

[1]Kovalchin et al., J Clin Pharmacol. 2011 May;51(5):649-60; [2]Kovalchin et al., J Neuroimmunol. 2010 Aug 25;225(1-2):153-63

Osteoarthritis – Focus on pro-anabolic approaches to benefit patients

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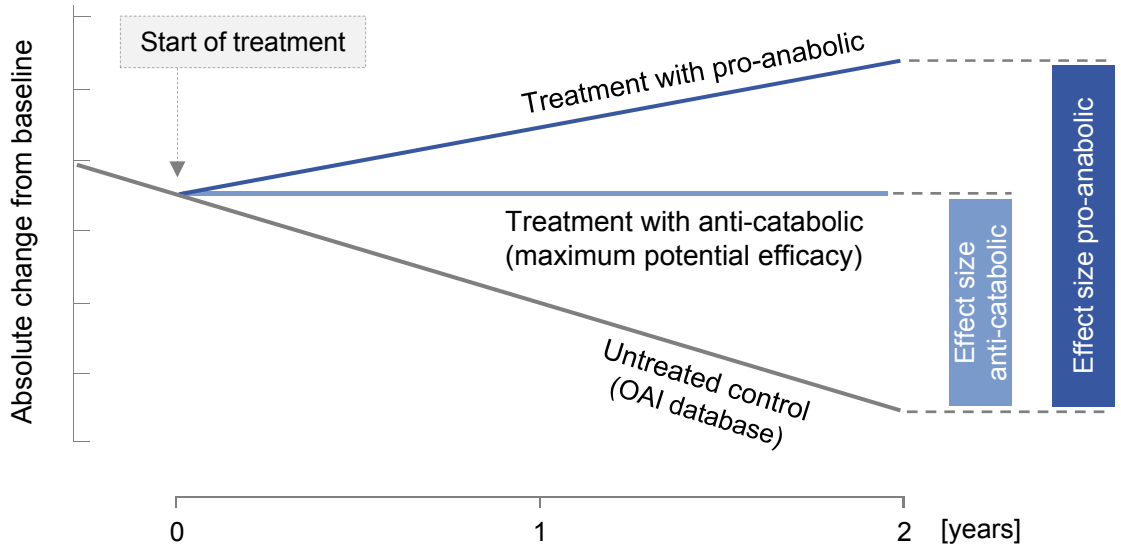
Change in cartilage on pro-anabolic versus anti-catabolic approaches



Anti-catabolic approach

- Halting cartilage breakdown
- Clinical benefit after >2 years

Pro-anabolic approach

- Growth & Replacement of cartilage
- Clinical benefit after ~1 year

OAI = Osteoarthritis Initiative

Phase Ib shows cartilage growth and perhaps need for longer observation times (>52 weeks)

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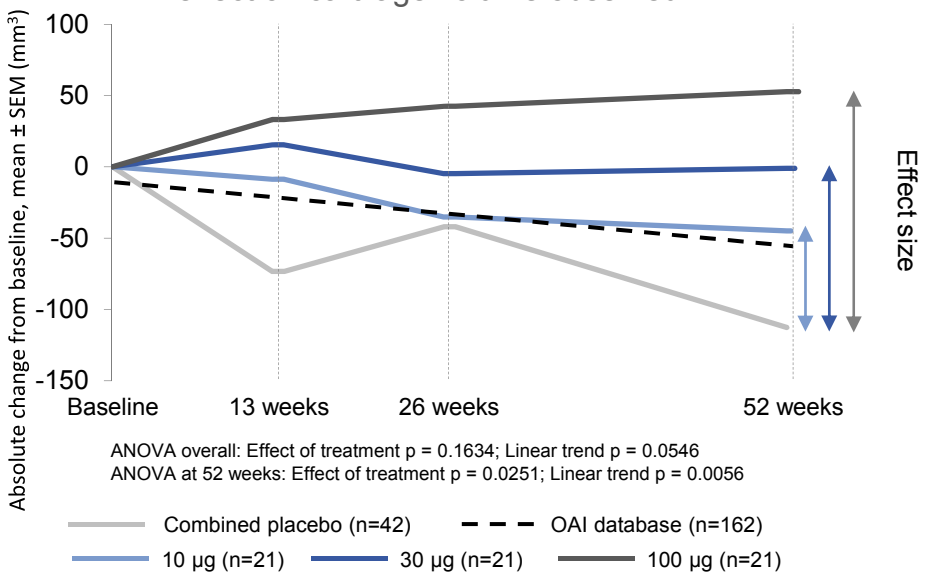
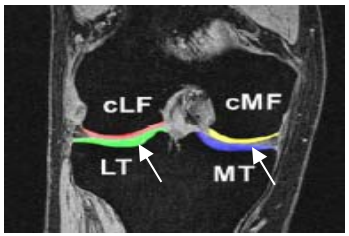
Structure results

At 52 weeks, dose-proportional, persistent anabolic effect on cartilage volume observed

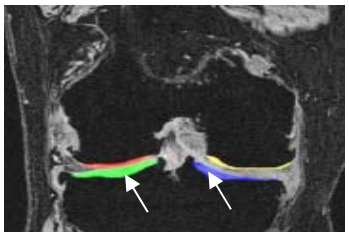


MRI examples

Patient A



Patient B



cLF = central lateral femora; cMF = central medial femora;
LT = lateral tibia; MT = medial tibia

Safety results

- No major local or systemic safety concerns during the course of the trial
- Slight trend for increased acute inflammatory reactions (AIRs), i.e. local knee pain and swelling up to 3 days following injections

ANOVA = analysis of variance; OAI = Osteoarthritis Initiative; MRI = magnetic resonance imaging
Source: Lohmander et al. Arth & Rheum, 2014

FORWARD: Observations extended to two-year endpoint with three-year follow up

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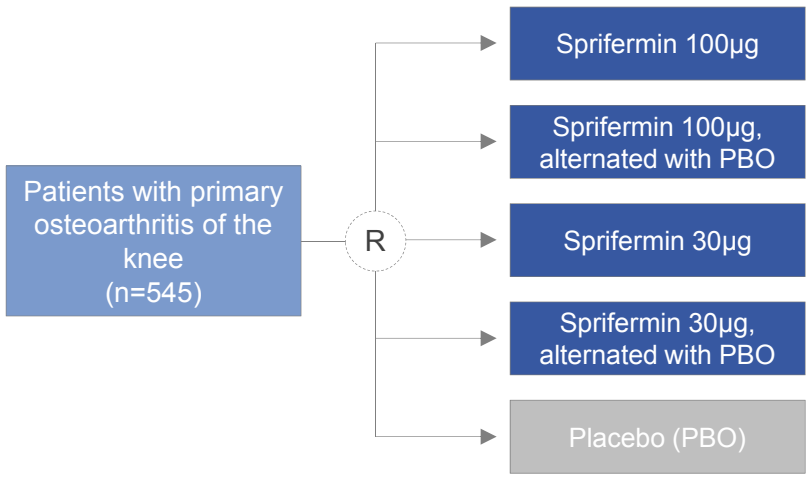
Phase IIb (FORWARD) trial design

Sprifermin

2-year, randomized, double-blind, placebo-controlled
4 cycles, each cycle includes 3 weekly injections over 3 consecutive weeks



Recruitment completed in Q2 2014
Data available in 2016

Phase II clinical trial enhancement

- Secondary outcome measure based on WOMAC score
- Explore two doses & two inter-cycle intervals
- Ultrasound-guided injections to ensure optimal drug delivery, potentially reduce post-injection AIRs
- Potentially select patients for Phase III based on biomarkers and/or other prognostic markers from Phase II

Strategic partnership with Nordic Bioscience

- Clinical development services in exchange for service fees, potential milestone and royalty payments
- Biopharmaceuticals retains full responsibility for the development and commercialization of the investigational drug
- Full enrollment of the planned 545 patients has already been achieved. Planned follow up continues

NORDIC BIOSCIENCE

WOMAC = Western Ontario and McMaster Universities Arthritis Index, used to assess the condition of patients with osteoarthritis of the knee and hip, including pain, stiffness, and physical functioning of the joints;
AIRs = acute inflammatory reactions

Summary

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- We have strong efficacy data on time-to-treatment flare and prevention of flare potentially supporting a differentiated profile in SLE with atacicept
- We aim to build a strong portfolio of autoimmune drugs, including a differentiated BTK inhibitor
- ATX-MS-1467 could be a first-in-class immunotolerizing agent in MS
- We continue to focus on pro-anabolic approaches for DMOAD activity in OA

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