GDF5 mutant R399E

a unique disease modifying development candidate in knee osteoarthritis and cartilage injury ready to start clinical development

- Multi-modal disease modifying development candidate for intra-articular administration in knee osteoarthritis (OA) and cartilage injury (CI), ready for phase 1 development in OA
- Potential first treatment option in knee OA to address sizable treatment gap between analgesics and knee replacement surgery with > 9 m eligible patients
- Animal models of surgically induced OA show unique improvement of symptoms and structure
  - Significant pain relief is achieved rapidly in 6 hours and is maintained over 12 weeks
  - Extrapolation of animal symptom data highlights potential for clinically meaningful effectiveness on pain in OA and CI
  - Demonstrated structural benefit based on anabolic and anti-catabolic properties
- Mode of action (MoA) allows accelerated clinical development in OA and CI based on early readout of symptom and structural endpoint
- "Pharma-grade" preclinical package developed by Merck KGaA, all rights with Biopharm
- Robust exclusivity period
- Management team of business and drug development experts with extensive pharmaceutical industry and indication experience

Value proposition

Growth and Differentiation Factor 5 (GDF5) is a protein of the Bone Morphogenetic Protein (BMP) family and is one of the few genes associated with OA. R399E is a single point mutation of GDF5 consisting of 119 amino acids and is expressed in *E. coli*.

Due to its multi-modal efficacy, R399E administered intra-articularly (i.a.), has disease modifying potential, i.e., to treat both symptomatic and structural issues associated with knee OA and CI.

Preclinical development has been performed by Merck KGaA up to phase 1 readiness. Merck decided to exit OA development focusing now on other strategic indications. Currently, Biopharm GmbH Merck´s initial licensor owns all rights on R399E. This creates the unique opportunity to invest into a phase 1 ready, "pharma-grade" development candidate.

Scientific rationale

R399E has a unique affinity profile for bone morphogenetic protein receptor type-1A (BMPR1A), BMPR1B and BMPR2 and induces intracellular signaling upon receptor binding. The drug candidate induces anabolic and anti-catabolic effects in 3D cultures of human OA chondrocytes (Fig. 1). R399E also inhibits the release of pain-inducing inflammatory molecules including IL1ß and PGE2 from synoviocytes, meniscal cells and chondrocytes.

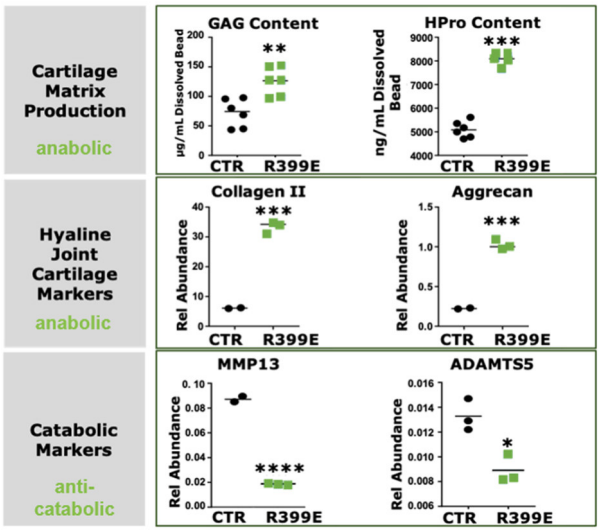

Fig. 1 Pro-anabolic and anti-catabolic effect of R399E

In vivo efficacy

Symptomatic benefit: R399E 6 µg i.a. induces significant and clinically relevant differences in Weight Bearing Pain compared to vehicle of 12.0-19.4 on 0-100 pain scale in a rabbit model of OA (Fig. 2), predicting favorable pain improvement in clinical trials of OA and CI.

Structural improvement: R399E i.a. prevents break-down of existing cartilage and promotes synthesis of new cartilage in rabbit and sheep OA models.

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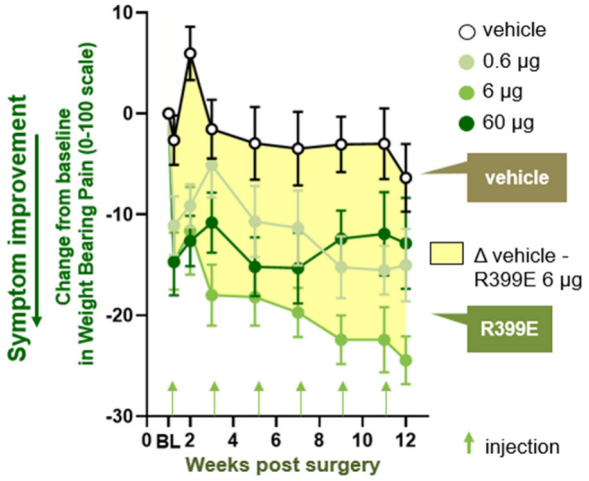

Fig. 2: Weight Bearing Pain has been calculated based on measurements of voluntary weight distribution in rabbits, in a model of surgically induced unilateral OA. Values were extrapolated to a scale of 0-100 to estimate potential of R399E to improve WOMAC pain.

Knee OA and cartilage repair – sizable markets with high unmet need

In knee OA, unmet need exists between acute symptomatic management and knee replacement surgery. By 2030 ~9 m target knees will be eligible for therapy with disease modifying OA drugs (DMOADs) in the 7 major markets (MM). Knee OA has been designated a 'priority disease' by WHO, being one of the ten most disabling diseases in developed countries.

Current therapies of knee OA are not sufficient. After initial conservative therapy, patients are treated with NDAIDs followed by opioids, duloxetine, i.a. cortisone or hyaluronic acid which all face challenges besides lack of structural and long-term symptom improvements. There are only a few drug candidates in development as DMOADs, but all of them have so far demonstrated only either symptom or structural improvement. Efficacy on pain and structure is necessary for DMOAD label and a multi-pathway approach as with R399E might be more promising to achieve efficacy and safety compared to single-target approaches.

Cartilage injuries of the knee lead to ~500k surgical procedures in 7MM. Significant unmet need is remaining and multi-modal R399E has potential to enable faster symptomatic improvement and better structural outcome.

Novartis initiated drug development in knee OA and CI with two clinical development programs clearing the way with authorities for late-stage clinical programs. This will undoubtedly generate interest in the pharmaceutical industry to enter these indications and will result in a demand for available attractive drug candidates.

Worldwide rights and robust exclusivity period

A composition of matter patent for R399E has been granted in major countries with an exclusivity period at least until 2032.

Next development steps

Upscaling to 60-100 l GMP batch scale both on USP and DSP. Set up of a phase 1/2 study in OA (32 patients planned) and phase 2 in CI (24 patients planned) with the potential to demonstrate symptom improvement (in knee OA and CI patients) and structural improvement in CI patients (early proof of concept).

Financing round series A

Why to invest

- R399E exhibit a unique combination of anabolic, anti-catabolic, anti-inflammatory and pain-reducing properties, with block-buster potential in unmet medical indications (OA and CI). Preclinical "pharma grade" package available, generated by Merck KGaA.
- distribution and minimization of risk with potential to demonstrate early proof of concept on symptoms and structure in two indications
- ideal competitive situation with Novartis paving the regulatory and clinical way for these neglected indications
- R399E has the chance to become a prominent acquisition target for pharma companies to enter financially attractive OA and CI markets

Biopharm GmbH a privately held biopharma-ceutical company is exploring options to further develop R399E.

We welcome further discussion.

For more information, kindly contact:

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