Galapagos NV (GLPG)
Rating: Buy

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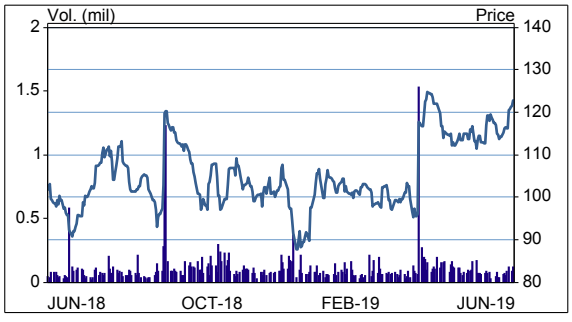
ROCELLA Is Off to a Running Start; GLPG1972 Recap

Stock Data	06/11/2019
Price	$122.75
Exchange	NASDAQ
Price Target	$150.00
52-Week High	$125.48
52-Week Low	$85.00
Enterprise Value (M)	$5,334
Market Cap (M)	$6,704
Shares Outstanding (M)	54.6
3 Month Avg Volume	119,251
Short Interest (M)	1.13
Balance Sheet Metrics	
Cash (M)	$1,369.6
Total Debt (M)	$0.0
Total Cash/Share	$25.08

Cash (M): Last reported cash balance during 1Q19 earnings was €1.22B.
General: Currency used is roughly 1 Euro to $1.12 US. Stock price is US$ as on NASDAQ

EPS (€) Diluted			
Full Year - Dec	2018A	2019E	2020E
1Q	€(0.73)	€(0.89)A	€(1.12)
2Q	€(0.42)	€(0.27)	€(1.14)
3Q	€0.27	€(1.17)	€(1.19)
4Q	€0.27	€(1.18)	€0.07
FY	€(0.56)	€(3.50)	€(3.37)
Revenue (€)			
Full Year - Dec	2018A	2019E	2020E
1Q	€44.8	€40.9A	€48.0
2Q	€57.0	€89.4	€48.0
3Q	€103.2	€43.0	€48.0
4Q	€112.8	€43.0	€118.8
FY	€317.8	€216.3	€262.8



Starting the data clock for an under-the-radar asset. On June 11, 2019, Galapagos disclosed the enrollment completion in the 850 patient Phase 2b, ROCELLA study. The ROCELLA program is a multi-regional, randomized, double-blind, placebo-controlled, dose ranging trial evaluating the safety and efficacy of three doses of GLPG1972 in patients with knee osteoarthritis (OA). GLPG1972 is orally administered, QD and has the potential to be a disease modifier for subjects with OA of the knee. ROCCELLA enrolled more than 850 patients in 12 countries in Europe, Asia, North and South America. Increase or maintenance of knee cartilage thickness quantified by MRI after 52 weeks is the primary outcome. Secondary objectives include safety and tolerability, and several additional measures of structural progression, pain, function, stiffness, and patient global assessment. GLPG1972, selectively inhibits the aggrecanase ADAMTS-5 believed to be responsible for significant degradation of cartilage during OA progression.

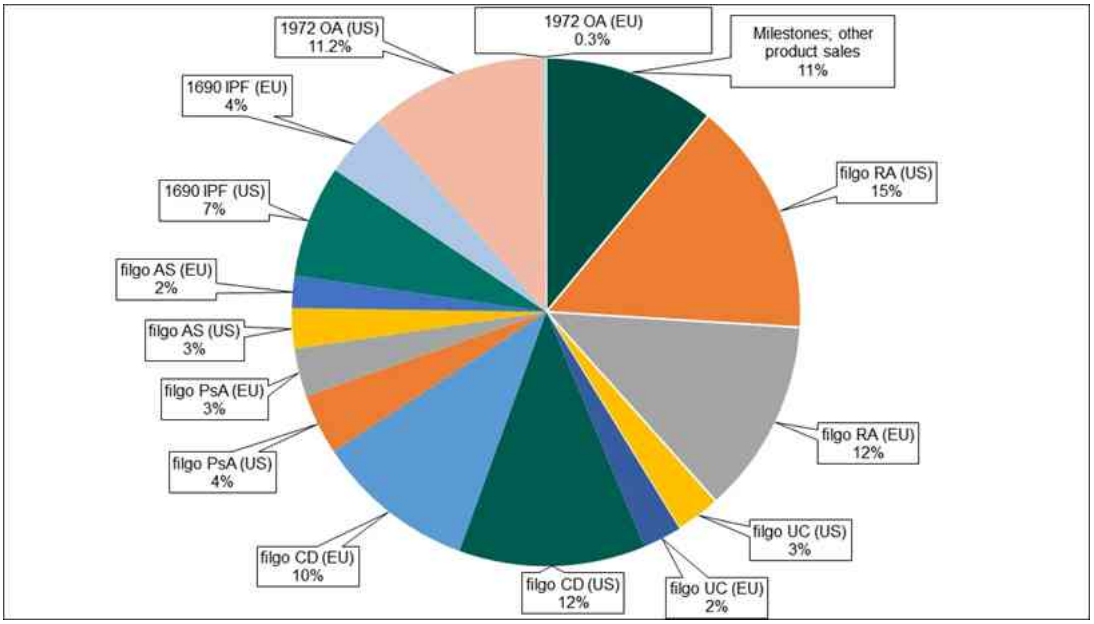
Pre-clinical and clinical data packages support the ROCELLA investment. *In vitro* data indicates potency and selectivity: (1) GLPG1972 inhibits ADAMTS-5 (IC_{50}<25 nM) exhibiting >5-fold increased IC_{50} for ADAMTS-4; (2) >150-fold increased IC_{50} for three other ADAMTS enzymes; and (3) >50-fold increased IC_{50} for six other MMPs. Selectivity of GLPG1972 decreases risk of AEs caused by MMP inhibitors that have previously failed in this setting. GLPG1972 administered at 10 µM reduced cartilage degradation >10-fold vs. untreated control, to wild-type levels, in human OA cartilage explant studies. GLPG1972 significantly reduced femorotibial cartilage proteoglycan loss and cartilage damage at all doses (33% at 120mg/kg BID) and subchondral bone sclerosis at all doses (36% at 120mg/kg BID) using the destabilization of the medial meniscus (DMM) mouse model. GLPG1972 was given at 1,050 mg QD for 14 days to healthy human subjects and serum ARGS levels decreased 60%. A small Phase 1b study of 24 patients found serum levels of ARGS decreased after 15 days of treatment with 300 mg GLPG1972 QD when compared to baseline, then resumed normal levels upon discontinuation.

ADAMTS-5; an interesting target, albeit with controversy. ADAMTS-5 activity correlates with OA progression and in human cartilage explants is required for ARGS formation. A literature review reveals that the degradation of cartilage is likely initiated by ADAMTS and MMP enzymes with ADAMTS-5 being the primary driver of the degradation, in our view. This is potentially validated by several observations, including: (1) in mouse cartilage explants stimulated by IL-1α, aggrecan fragment release was dependent on ADAMTS-5 catalytic activity. However, the precise cytokine responsible for stimulating cartilage degradation in humans is unknown; (2) in OA patients, baseline expression of ADAMTS-5 expression has been positively correlated with OA progression; and (3) a prior peer attempt at engaging the target with a specific ADAMTS-5 inhibitor (IC_{50}=30 nM) inhibitor, reduced ARGS release by 50% in a human OA cartilage explant. However, we note serum-ARGS as a surrogate for aggrecanase activity might have limitations in quantifying OA progression.

ARGS might not be the best biomarker of OA progression; for a deeper dive, refer to pages 6 to 22. OA is a degenerative disease believed to be driven by cytokine induced cartilage loss which leads to bone spurs and subchondral bone thickening. Aggrecan and collagen are the most abundant components of cartilage. The ADAMTS-5 enzyme cleaves aggrecan at E373-374A site to release the DIPEN fragment, and matrix metalloproteinases susbequently cleave aggrecan to release NITEGE and ARGS fragment. DIPEN, NITEGE, and ARGS fragments are released into synovial fluid and serum and have been used as biomarkers of OA progression. Unfortunately, serum or synovial fluid ARGS fragments do not correlate with OA disease status, nor do ARGS fragments increase with age which is contrary to increased incidence of OA with advanced age. Additionally, serum ARGS fragments could originate in tissues besides knee joints. However, in cartilage explants, OA patients produce ARGS fragments while healthy individuals do not. To reconcile these observations, we hypothesize that ARGS fragments may be degraded rapidly. We note key risks to the development of GLPG1972: (1) ADAMTS-4 and -5 are expressed in multiple tissues throughout the body hence, the long term repercussions of aggrecanase inhibition are not known. Cynomologous monkeys treated with GSK239400, an ADAMTS-5 antibody, developed cardiovascular problems possibly due to degradation of versican. However, ADAMTS-5-/- and ADAMTS-4-/- mice are viable indicating this may not be too great a concern; (2) pre-clinical data supporting ADAMTS-5 inhibitor's *in vivo* efficacy is primarily based on an unreliable mouse model; DMM. The DMM mouse model is an acute injury model, which can show high levels of ARGS formation, unlike in humans, and may not mimic the slow progression of OA; (3) cartilage explant studies supporting ADAMTS-5 efficacy may be flawed, in our view. For example, ARGS formation in cartilage explants is induced by IL-1B or TNF-alpha treatment, however inhibition of these signaling pathways has not been successful in clinical trials, and ADAMTS-5 mRNA is not regulated by cytokines; and (4) a similar small-molecule ADAMTS-5 inhibitor, by GSK (GSK; not rated), was discontinued potentially due to limited half-life of 0.6 hrs and low oral bioavailability of 1.5%. Note, the half-life of GLPG1972 is 10 hrs.

Valuation and risks to our investment thesis. Our 12-month, $150 price target on shares of Galapagos is derived from a 13-year DCF-based, sum-of-the-parts analysis. Our DCF is driven by: beta of 1.34, terminal growth rate of -3.0%, risk premium of 4.93%, calculated WACC of 9.3%, and tax rate of 20% beginning in FY 2025. Filgotinib (66%), GLPG1690 (11%), GLPG1972 (11%) together make up 88% of our value, with the remainder derived from the probability-adjusted, filgotinib-associated milestone payments. For filgotinib, we assume POS in the range of: 75% (upped from 65% previously) for RA based on the FINCH 1 and 3 clinical updates released post close on March 28, 2019, 65% for UC, and 60% for CD, PsA and AS each, whereas for '1690 and '1972, we assign a 35% and 10% POS, respectively. Note, filgotinib, in our view, did not materially underperform upadacitinib in the FINCH 1 and 3 studies, which we assigned a low probability outcome due to its competitive profile, along with our $2.9B in 2027 sales estimate for the RA segment. Other key risks include: emergence of safety concerns, clinical risks, regulatory risks, and financial risks. Furthermore, regulatory and commercial strategy for filgotinib is under the control of partner, Gilead, not an established player in autoimmune indications. Hence, Gilead may not be able to drive rapid adoption of filgotinib, especially if the overall profile is relatively undifferentiated from AbbVie's upadacitinib, in our view. Hence, our estimates could be negatively impacted if AbbVie successfully leverages its market positioning with Humira during the launch of upadacitinib, which is likely to be a year ahead of filgotinib. The next two value drivers for Galapagos are GLPG1690 and GLPG1972 programs, both of which are high-risk, high-reward programs given the checkered history of drug development of each target. Hence, there are significant clinical risks associated with these programs, which we believe are adequately reflected in our POS assumptions.

Exhibit 1: Weighted Contribution of Individual Disease Segments to Target



Source: H.C. Wainwright & Co. estimates.

GLPG1972 as a Disease Modifying Therapy for Osteoarthritis

Overview of Osteoarthritis (OA) and Clinical Opportunity for GLPG1972

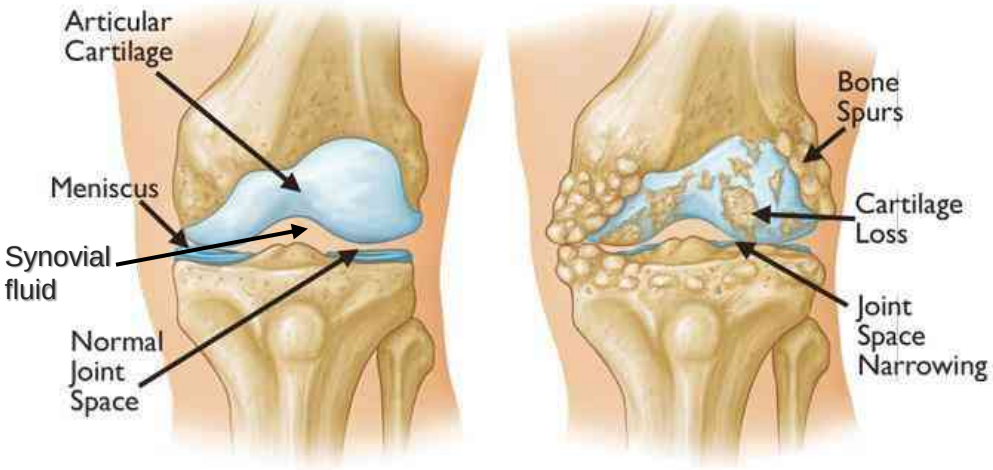
- **No DMOAD approved**
- **GLPG1972 targets ADAMTS-5, aggrecanase, to reduce cartilage degradation**
- **Serum and SF ARGS measurements are not good indications of OA**
- **Cartilage is degraded, and ARGS fragments are produced from OA tissue**
- **ADAMTS-5 activity inhibits mouse knee injury recovery**
- **ADAMTS activity is correlated with OA progression**
- **ADAMTS inhibition reduces ARGS release in OA explants**
- ***In vitro* data is positive for GLPG1972**
- **Competition from Merck's Sprifermin, far ahead in trials, shows promising results**
  - **However, requires intra-articular injections**

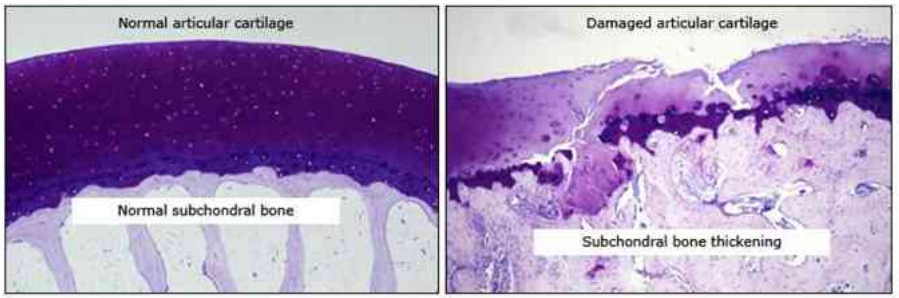
OA Background

- **Affects 240M worldwide**
- **No disease-modifying drugs approved**
- **Bone spurs**
- **Subchondral bone thickening**
- **Cartilage loss (degradation of aggrecan)**
- **Pathogenesis driven by cytokines**
- **Degenerative disease**

- **GLPG1972 is a small molecule inhibitor of ADAMTS-5 aggrecanase**

- **GLPG1972 program focuses on OA of the knee**





Source: UpToDate, Inc and American Academy of Orthopaedic Surgeons.

Why Target ADAMTS5? It Cleaves Aggrecan and is Linked to Cartilage Degradation

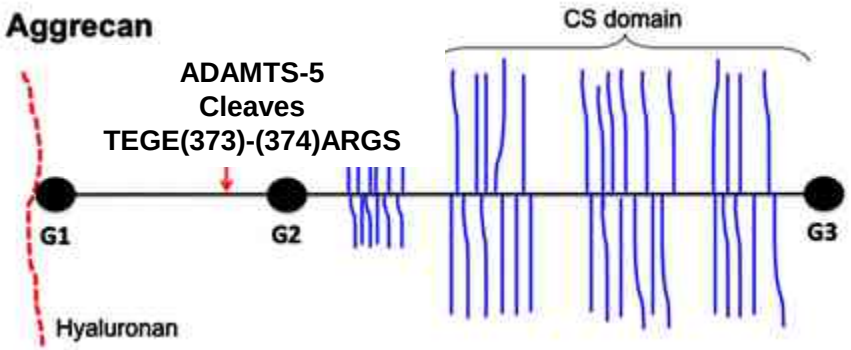
Aggrecan and collagen are most abundant components of cartilage

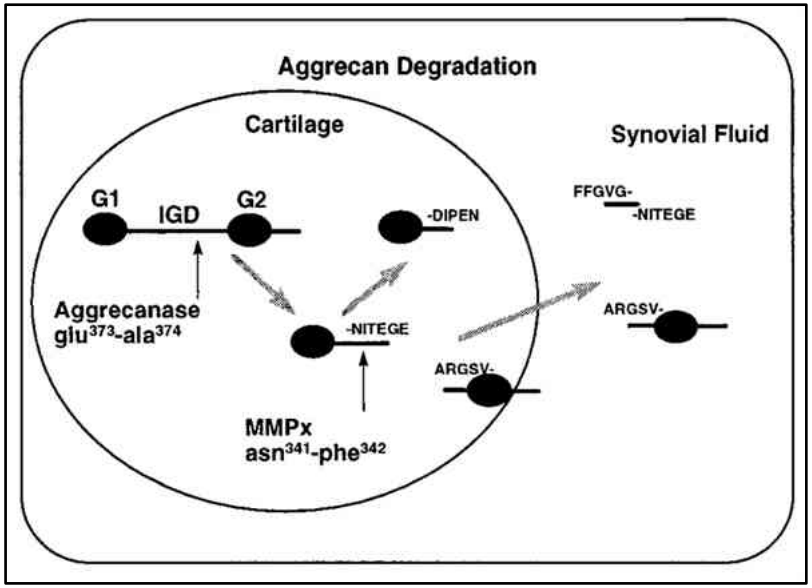
ADAMTS-5 enzyme cleaves aggrecan at E373-374A site to release DIPEN fragment

Subsequently MMPs cleave aggrecan to release NITEGE and ARGS fragment

DIPEN, NITEGE, and ARGS fragments are released into synovial fluid and can be a markers of aggrecan degradation

GLPG has reported decreased serum ARGS resulting from GLPG1972 treatment in humans

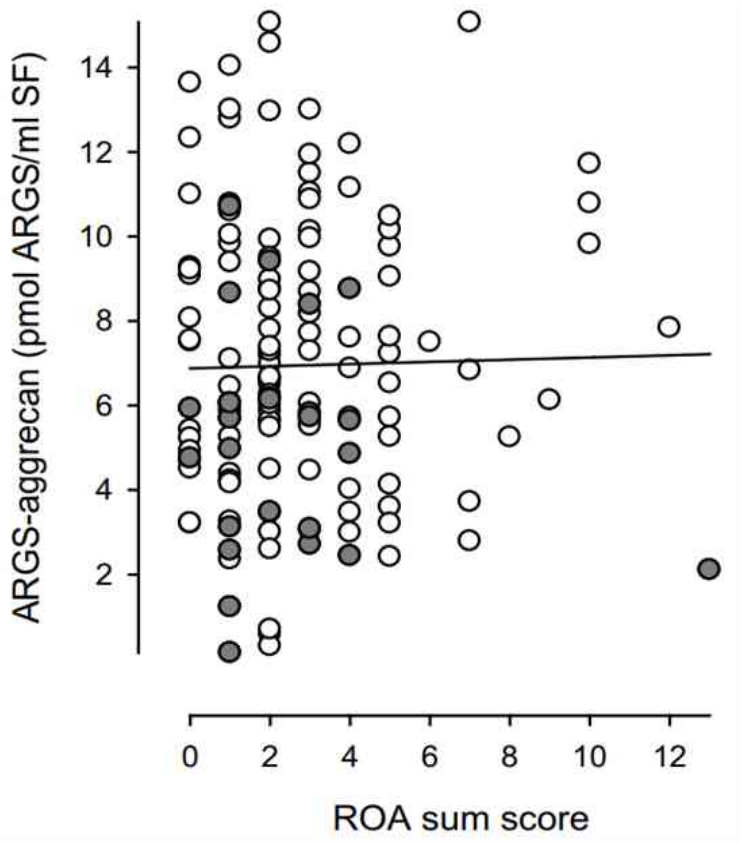




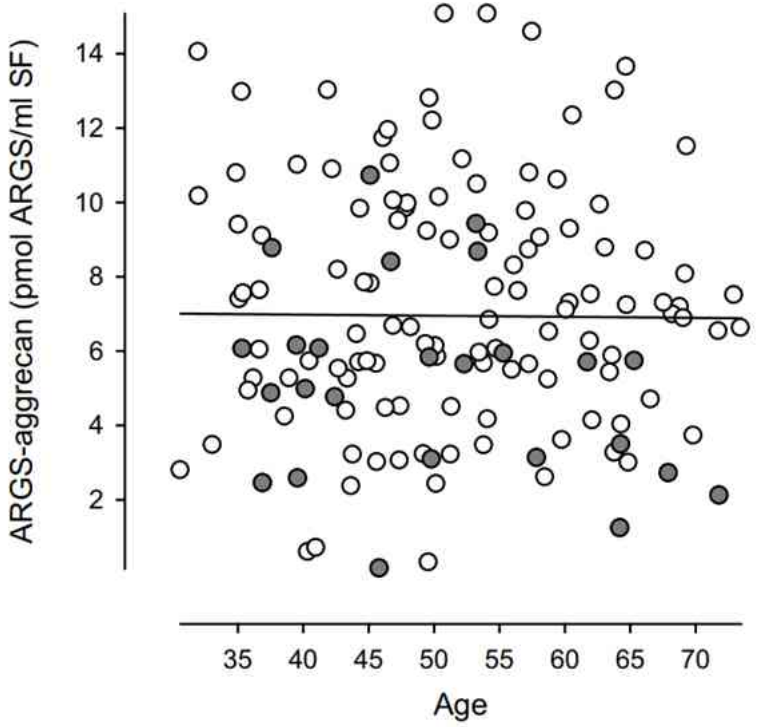
Source: Modified from Biochemical Journal, 2015 (473) DOI: 10.1042/BJ20151072.

Words of Caution on Serum ARGS as a Marker– No Direct Correlation to OA

Synovial fluid ARGS fragments do not correlate with OA condition



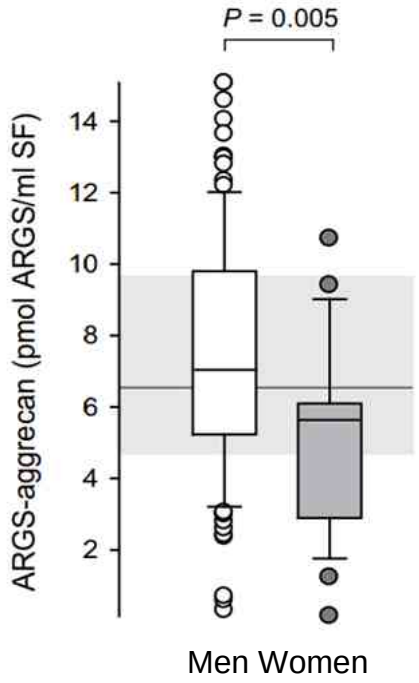
No accumulation of ARGS fragments over time



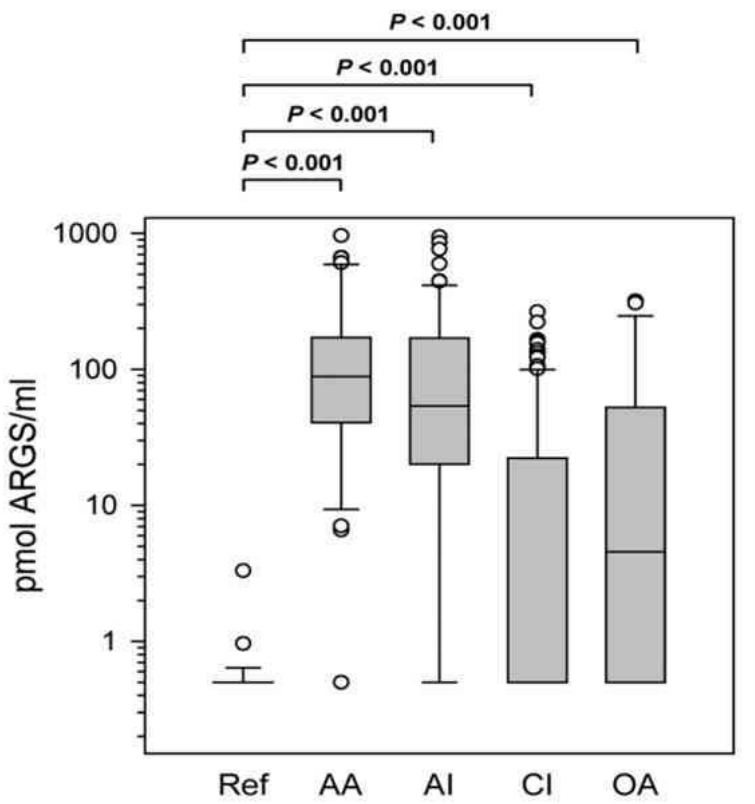
Source: Arthritis Research & Therapy 2010 (12:R230) DOI: 10.1186/ar3217.

Serum ARGS as a Marker–Correlates With Gender, but Not Underlying Disease

Men have higher amounts of ARGS, but women have a higher incidence of OA



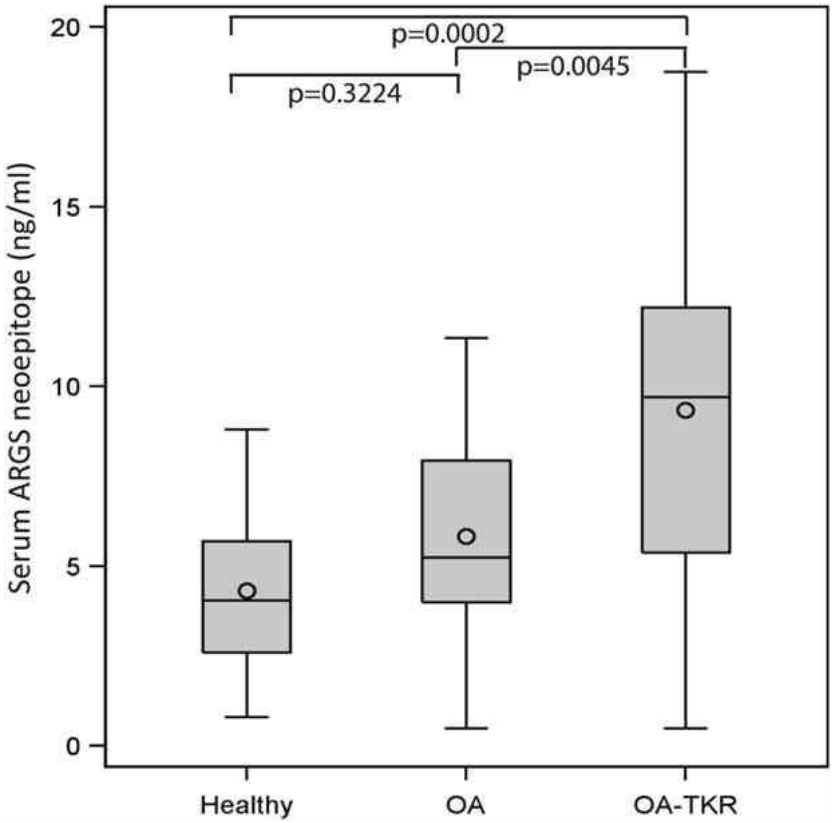
Acute injuries show high levels of ARGS while chronic conditions show lower levels of ARGS



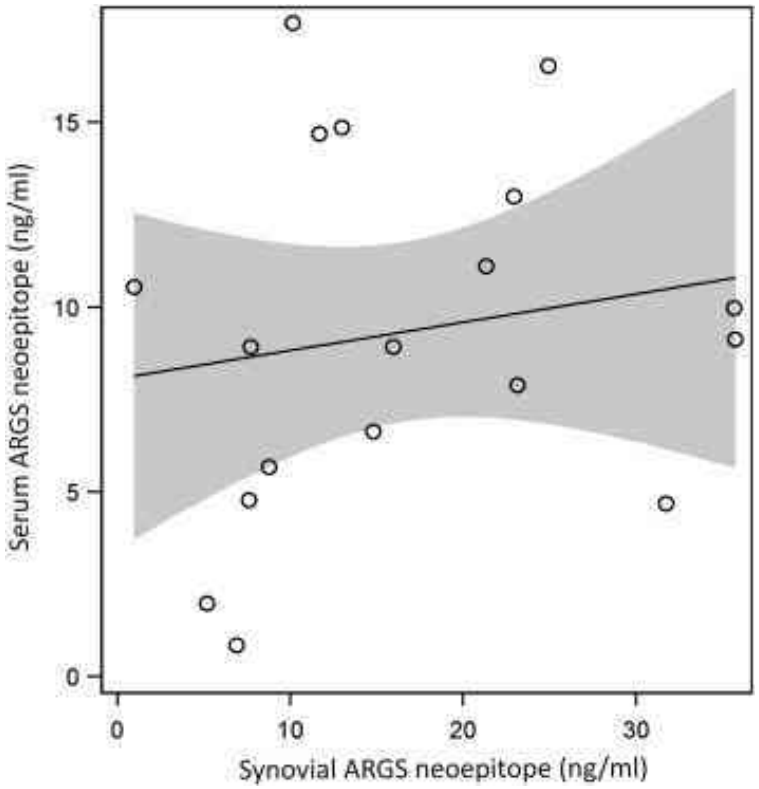
Source: Arthritis Research & Therapy 2010 (12:R230) DOI: 10.1186/ar3217 and Arthritis Rheum. 2008 (58;1) DOI: 10.1002/art.23176.

Bottom line—Serum ARGS Might Not Be the Best Marker for OA

No difference between OA and healthy patients



Serum ARGS does not correlate with synovial ARGS

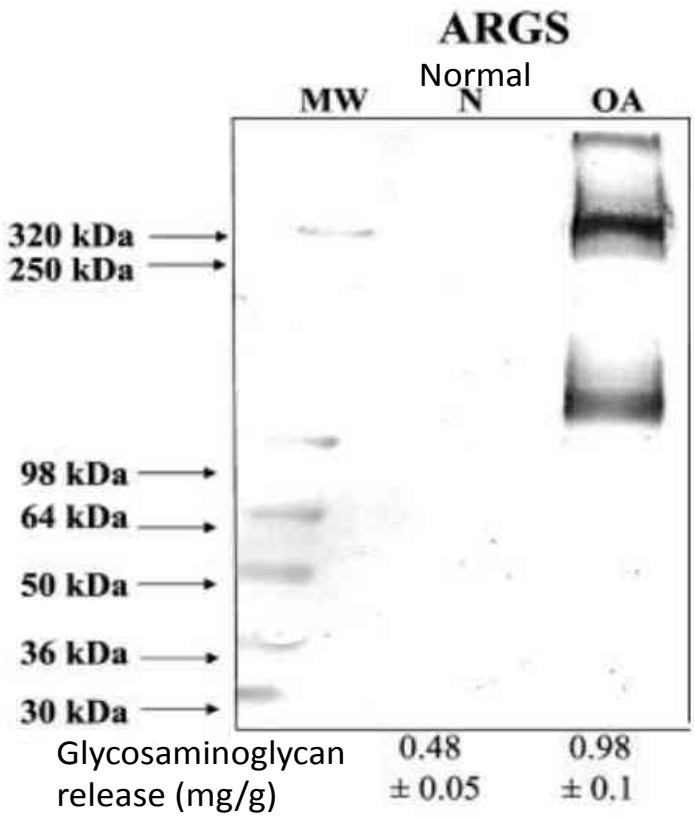


Source: Osteoarthritis and Cartilage 2014 (22;5) DOI: 10.1016/j.joca.2014.02.930.

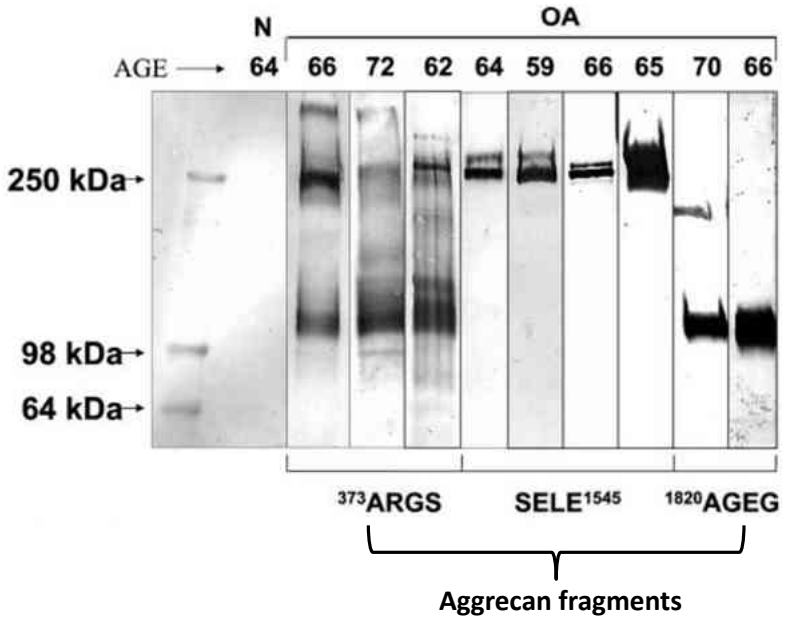
Lack of Correlation With Serum ARGS Does Not Make ADAMTS5 a bad Target, in our View

Synovial Fluid Measurements Paints a Different Picture on ARGS in OA

In cartilage explants, OA patients produce ARGS fragments while healthy individuals do not

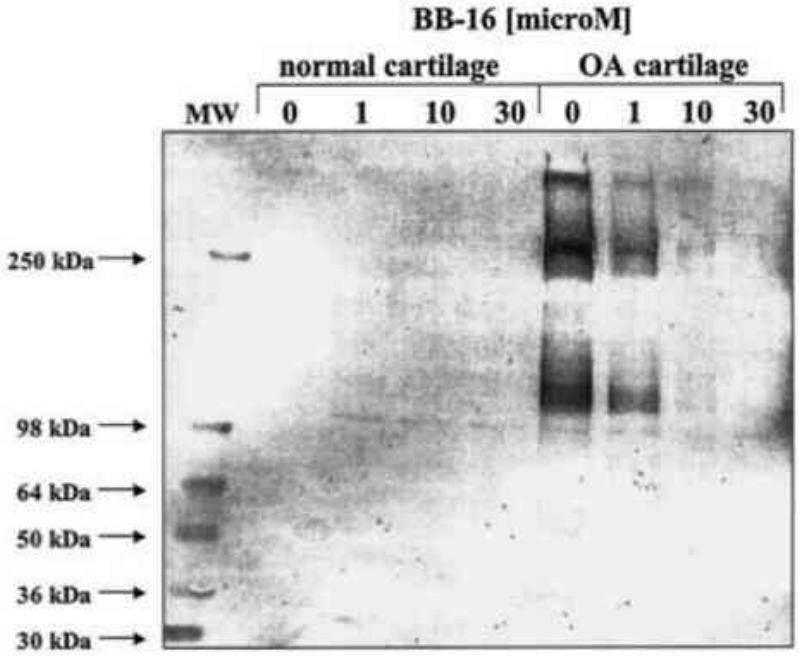


OA patients produce ARGS fragments while Normal patients do not



Source: Journal of biological chemistry 2002 (277;25) 2002 DOI: 10.1074/jbc.M200431200.

While MMP's and ADAMTS' Are Both Responsible for ARGS, MMP Inhibitors Have Failed in Clinical Trials



Source: Journal of biological chemistry 2002 (277;25) DOI: 10.1074/jbc.M200431200 *and https://search.proquest.com/docview/215110594.*

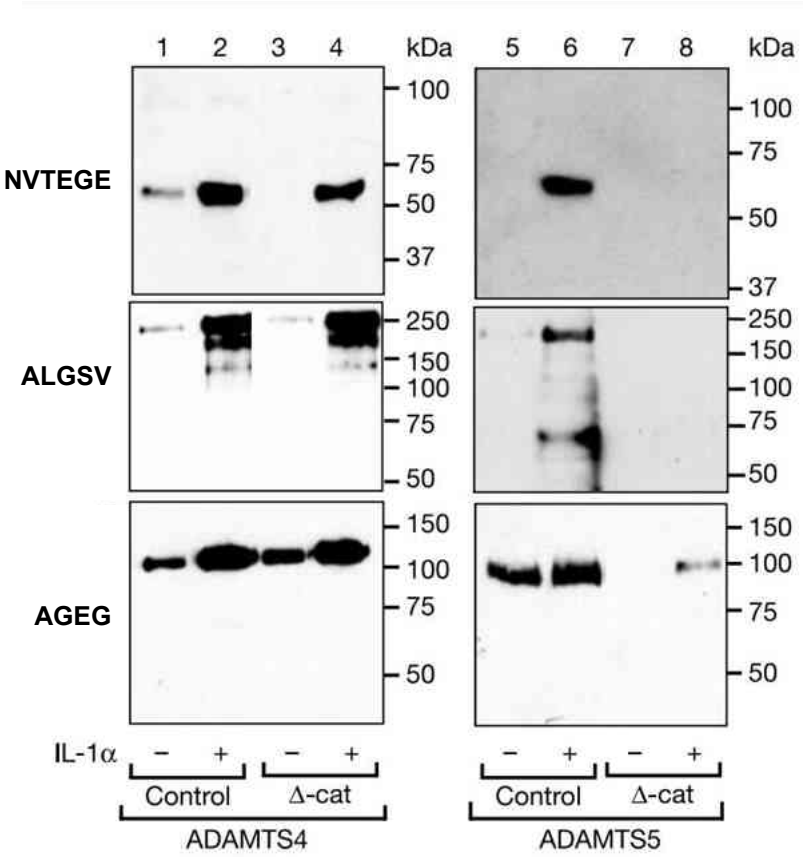
- **Cartilage explants from normal and osteoarthritic patients were cultured, not induced by cytokines, and media were treated with differing amounts of BB-16 (inhibitor of MMPs and ADAMTS-4,5)**
- **ARGS was detected by western blot**
- **OA patients produce ARGS fragments while Normal patients do not**

Our Take—It Might Well Be ADAMTS5

- **Serum ARGS measurements are not a good indicators of OA**
- **Cartilage is degraded during OA, and ARGS fragments are produced from OA tissue**
- **Suggests that ARGS are probably degraded or re-integrated rapidly**
- **While ADAMTS and MMP might both be responsible, as elaborated upon subsequently ADAMTS5 might be the primary driver of the degradation, in our view**

ADAMTS-5 Activity Is Required for Aggrecan Release in Mice

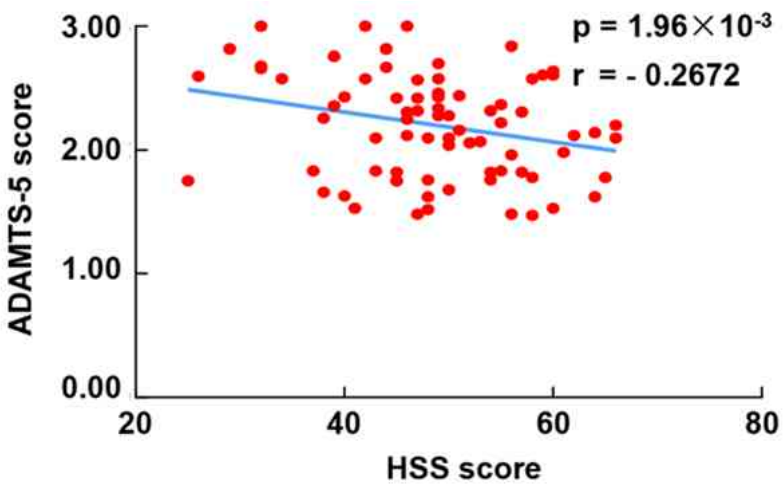
- **IL-1α stimulates mouse cartilage explants to release different aggrecan fragments**
- **Release dependent on ADAMTS5 catalytic activity**
- **However, the precise cytokine responsible for stimulating cartilage degradation in humans is unknown**



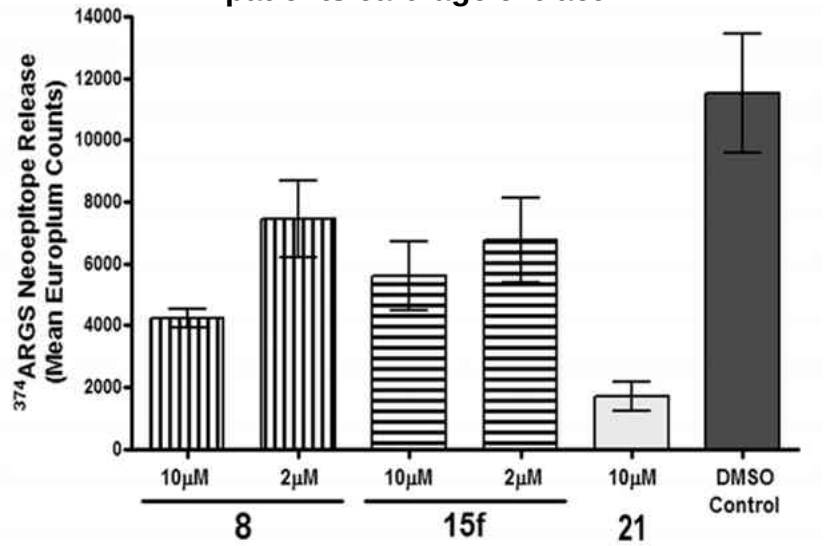
Source: Nature, 2005 (434) https://www.nature.com/articles/nature03417.

ADAMTS5 Expression and Inhibition Correlates With ARGS Activity—Bodes Well for GLPG1972

ADAMTS-5 expression is positively correlated with worse OA diagnosis



ADAMTS-5 inhibition reduces ARGS release in OA patients cartilage extract



Source: J Mol Med 2016 (94) DOI: 10.1007/s00109-016-1418-z and Journal of medicinal chemistry 2012 (55;16) DOI: 10.1021/jm300449x.

- **Compound 15f is a specific ADAMTS-5 (IC_{50}=30 nM) & ADAMTS-4 (IC_{50}=1300 nM) small molecule inhibitor developed by GSK**
- **15f inhibits ARGS release by 50% in a human OA cartilage explant**
- **Compound 21 is a non-specific MMP inhibitor reduces ARGS by 83%**
- **GLPG1972 has lower IC_{50}s**

Our Take—ADAMTS5 Inhibition With GLPG1972 Might Correlate With Disease Stabilization

- **Cartilage is degraded by ADAMTS-5 and ARGS fragments are produced in joints**
- **ADAMTS-5 activity inhibits mouse knee injury recovery**
- **ADAMTS-5 activity is correlated with OA progression**
- **ADAMTS inhibition reduces ARGS release in OA explants**
- **GLPG1972 has lower IC50s compared to the discontinued GSK effort, 15f**

GLPG1972 Progress to Date and the Ongoing 852 Patient ROCELLA Phase 2 Program

April 2017

- **GLPG1972 significantly reduced femorotibial cartilage proteoglycan loss and cartilage damage at all doses (39% at 120mg/kg BID) and subchondral bone sclerosis at all doses (36% at 120mg/kg BID) using the destabilization of the medial meniscus (DMM) mouse model**

June 2017

- **GLPG1972 inhibited the IL-1β stimulated degradation of human cartilage explants.**
- **GLPG-1972 inhibited ADAMTS-5 (IC50=20 nM) and ADAMTS-4 (IC50=57 nM) in vitro**

April 2018

- **GLPG1972 was given at 1050mg QD for 14 days and serum ARGS levels decreased**

June 2018

- **A small Phase 1b study of 24 patients found serum levels of ARGS decreased after 15 days of treatment with 300 mg GLPG1972 QD compared to baseline**

ROCELLA

- **Multi-center, randomized, double-blind, dose ranging trial evaluating efficacy and safety of 3 different (unknown) doses of GLPG1972 in 852 knee OA patients**
- **Primary objective is to reduce cartilage loss after 52 weeks treatment**
- **Secondary objectives are safety, tolerability, structural progression, pain, function, and a global assessment**
- **Estimated completion date is 2H20**
- **Our model incorporates a 10% probability of success for GLPG-1972, which is based on the limited clinical data, despite the ongoing 852 patient Phase 2 program**
- **We value GLPG-1972 at $16 per share, but given the large unmet clinical and commercial need, a positive Phase 2 readout points with clear correlation between ADAMTS5 inhibition and OA symptom modulation implies meaningful upside to our estimates**

Sources: DOI: 10.1136/annrheumdis-2017-eular.3775 https://www.oarsijournal.com/article/S1063-4584(18)30723-4/pdf DOI: 10.1136/annrheumdis-2018-eular.3101 https://www.oarsijournal.com/article/S1063-4584(17)30155-3/pdf

Risks on the ADAMTS-5 target

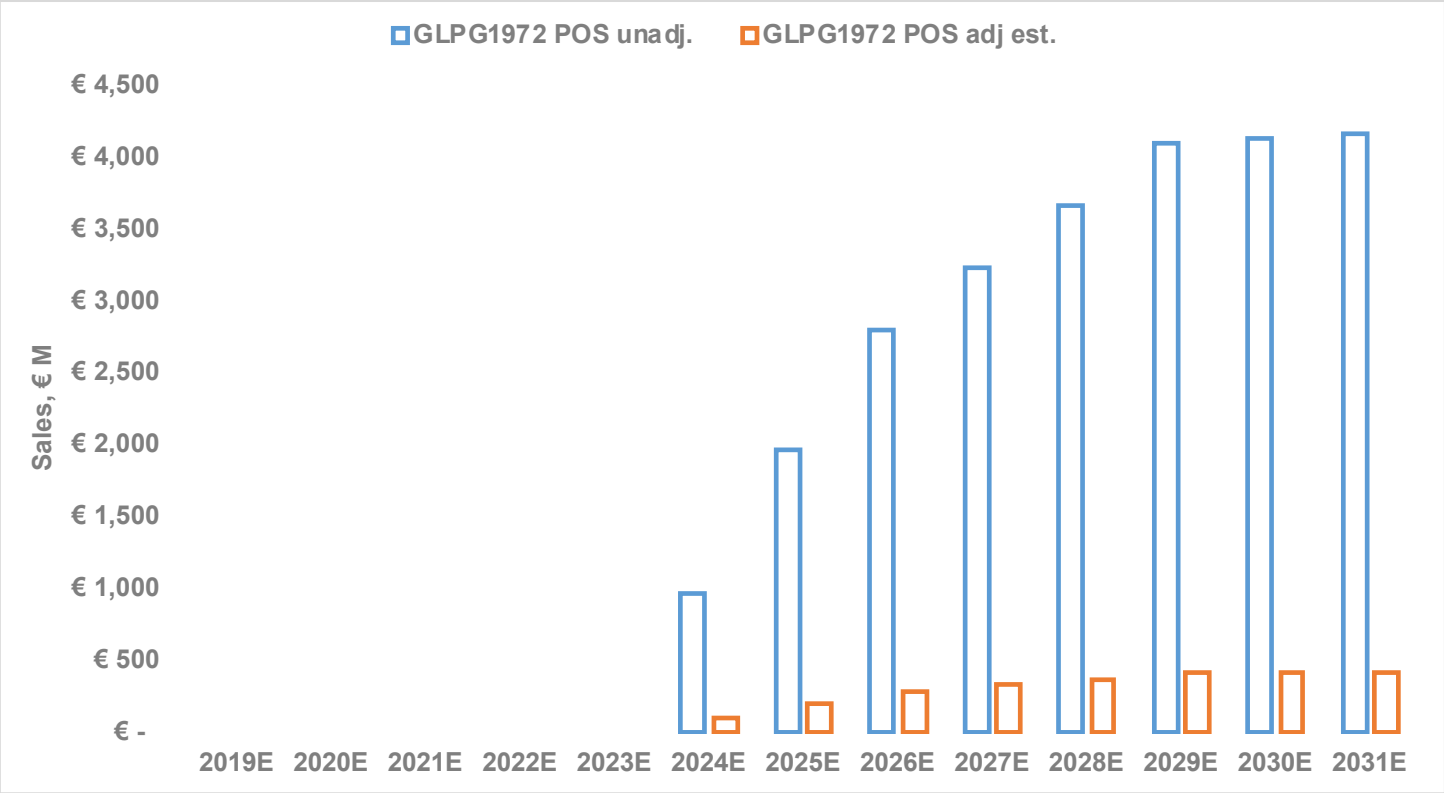
- **Selectivity for ADAMTS family is essential. Several MMP inhibitors have failed because of adverse muscoskeletal effects, with symptoms beginning to show after 3 months. Thus it is important that ADAMTS inhibitors only effect aggrecanases. Seems GLPG1972 is acceptable here**
- **ADAMTS-4 and -5 are expressed in multiple tissues throughout the body. The long term repercussions of aggrecanase inhibition is not known. Cynomologous monkeys treated with GSK239400 an ADAMTS-5 antibody developed cardiovascular problems possibly due to degradation of versican. However, ADAMTS-5-/- and ADAMTS-4-/- mice are viable indicating this may not be too great a concern**
- **Use of urine, serum ARGS levels as a surrogate marker for aggrecanase activity is probably unreliable, and at worst could be a contraindication for OA improvement. Serum ARGS fragments could originate in tissues besides knee joints. A better marker could be ADAMTS-5 protein expression in synovial fluid, as this has been correlated with OA condition**
- **DMM mouse model is an acute injury model, which can show high levels of ARGS formation, unlike in humans, and may not mimic the slow progression of OA. The data indicating ADAMTS-5 inhibitors *in-vivo* efficacy is mostly based on this mouse model. The inhibition of ARGS fragment formation from uninduced OA human cartilage explants may be a better model. Induction of ARGS formation via IL-1B or TNF-alpha, may not be a great model because inhibitors of these signaling pathways have not been successful in clinical trials, and ADAMTS-5 mRNA was not regulated by cytokines**
- **GSK made a small-molecule ADAMTS-5 inhibitor that was not pursued due to low half-life (0.6 hrs), low oral bioavailability (1.5%). The half-life of GLPG1972 is 10 hrs, but the oral bioavailability of GLPG1972 is not reported.**
- **Sprifermin by Merck (MRK; not rated) could cut into market share. Sprifermin is a recombinant hFGF-18 peptide administered by knee injection, currently in 5th year of Phase II study in 549 OA patients. Reports are for stat sig dose-dependent increase in cartilage thickness, and at highest dose, the improvement is maintained 18 months after treatment stopped, and an acceptable safety profile.**

Source: *Abstracts / Osteoarthritis and Cartilage 2014 (22)*
https://www.oarsijournal.com/article/S1063-4584(14)00958-3/pdf

Why '1972 could work

- **GLPG1972 has high selectivity for ADAMTS-5 & 4, much greater than MMPs. This limits the risk of musculoskeletal problems and is supported by Phase 1b patients exhibiting no AEs.**
- **'1972 has lower IC_{50}s than a compound that significantly reduced cartilage degradation in human explants.**
- **ADAMTS-5 expression is correlated with OA progression**

GLPG1972 POS-Adjusted and Unadjusted Estimates



Source: H.C. Wainwright & Co. estimates.