Efficacy of the highly selective ADAMTS-5 inhibitor GLPG1972 in the rat meniscectomy model

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EULAR 2018, Amsterdam
15 June 2018

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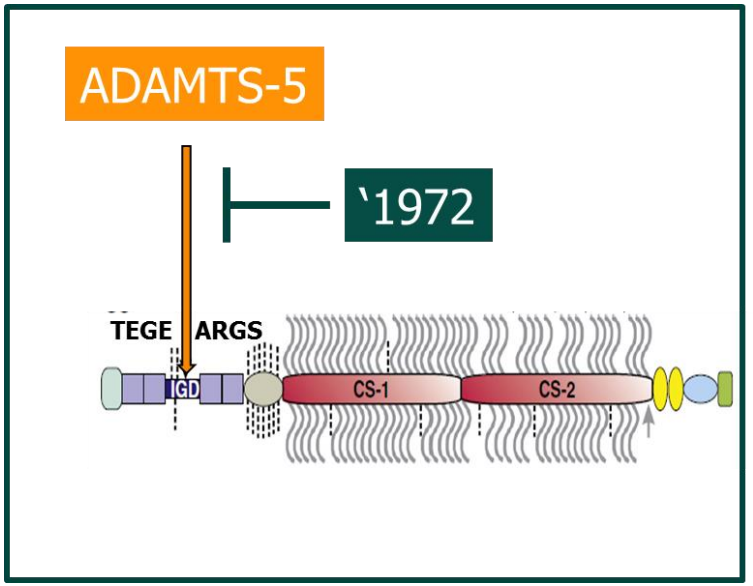
DISCLOSURES

- I am a Galapagos employee

ADAMTS-5
a promising therapeutic target in OA

- ADAMTS-5 plays a key role in aggrecan degradation in OA
- Strong literature evidence for ADAMTS-5:
  - Validated in human OA cartilage explants[1]
  - adamts-5$^{-/-}$ mice were protected from cartilage degradation and mechanical allodynia in DMM model[2]
  - Mice treated with ADAMTS-5 mAb had attenuated joint damage and were protected from mechanical allodynia[3]
  - ARGS levels increased in human knee synovial fluid in OA[4]



Source: [1] Song, 2007; [2] Glasson, 2005 & Malfait, 2010; [3] Miller, 2016; [4] Larsson, 2009

'1972 Profile

	GLPG1972
h-ADAMTS-5 potency (IC_{50} nM)	**<25**
r-ADAMTS-5 potency (IC_{50} nM)	**<25**
h-ADAMTS-5 (Aggrecan-ELISA) (IC_{50} nM)	**<70**
Selectivity against other proteases	**High**
GAG release inhibition in **mouse** cartilage explants (IC_{50} nM)	**<1,500**
AGNx1 release inhibition in **human** cartilage explants (IC_{50} nM)	**<1,000**
Mice DMM model (oral administration)	**DMOAD activity**

Source: EULAR 2017, Madrid

Rat MNX: experimental design

Treatment period (p.o.) from D2 to D21

D0 — D1 — D12 — D21

Meniscectomy right knee

Randomization

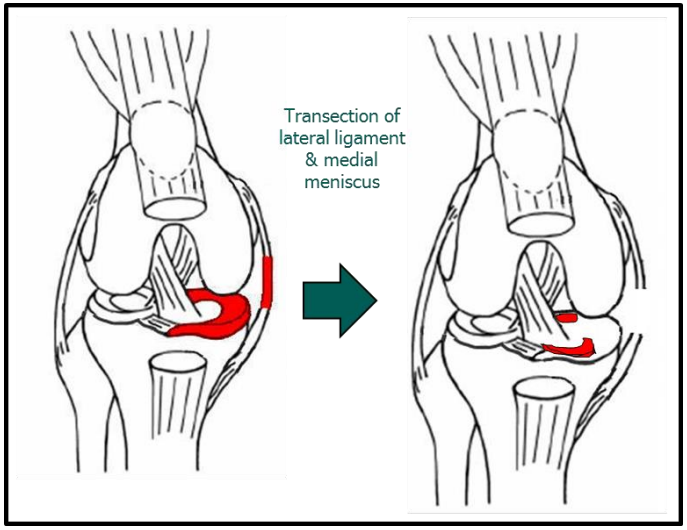
ssPK

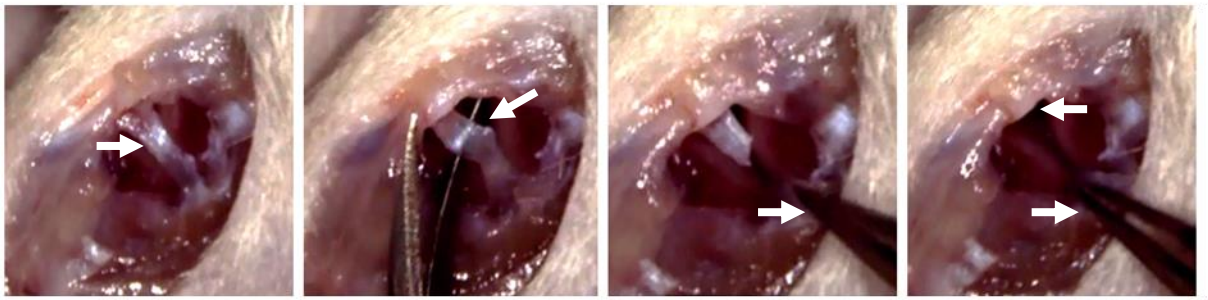
Sacrifice

Plasma + femoral condyle cartilage for compound exposure (n=5/group)

Right tibia for OARSI scoring + secondary readouts (n=20/group)

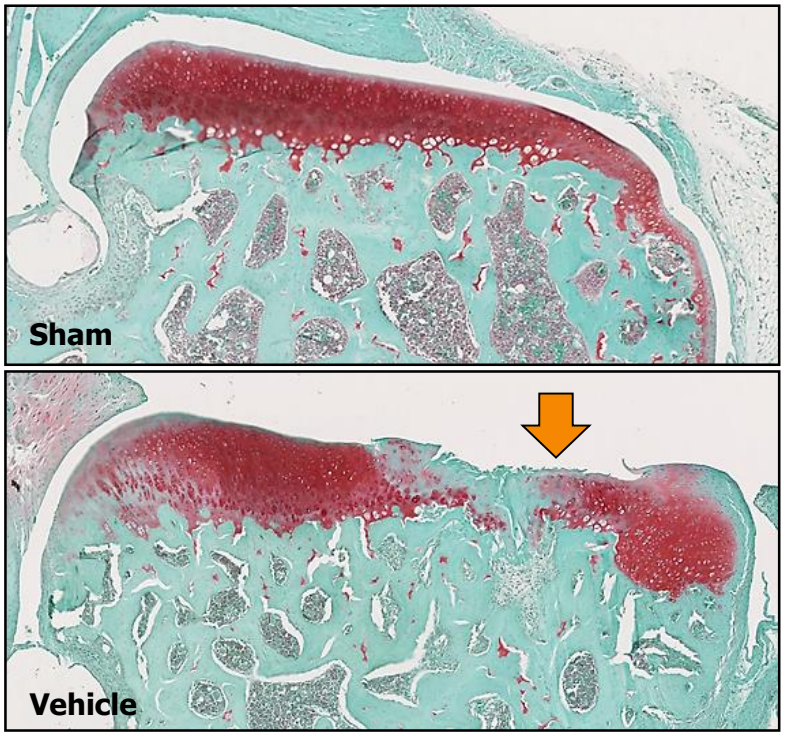
Female Lewis rats n=20/group

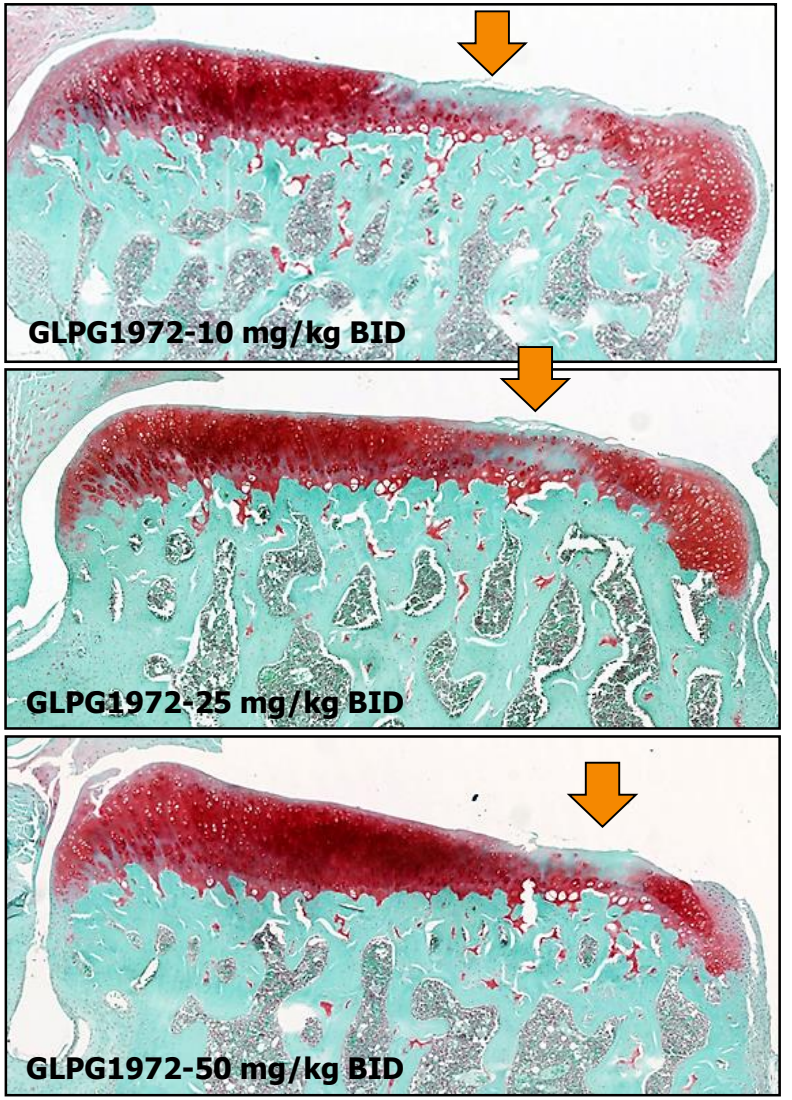




meniscus | **Cut of meniscus** | **Push back** | **Final meniscectomy**

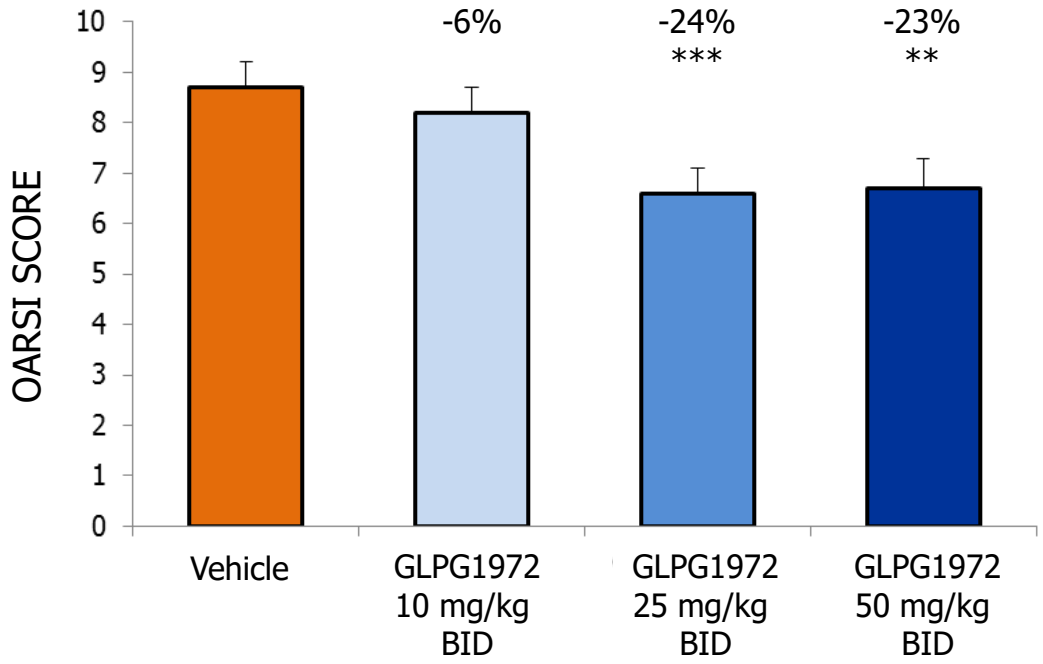
‘1972 restores cartilage in the tibial plateau





Rat tibia long section
Eroded area on medial plateau with (arrow)
Safranin O – light green staining
Magnification x25

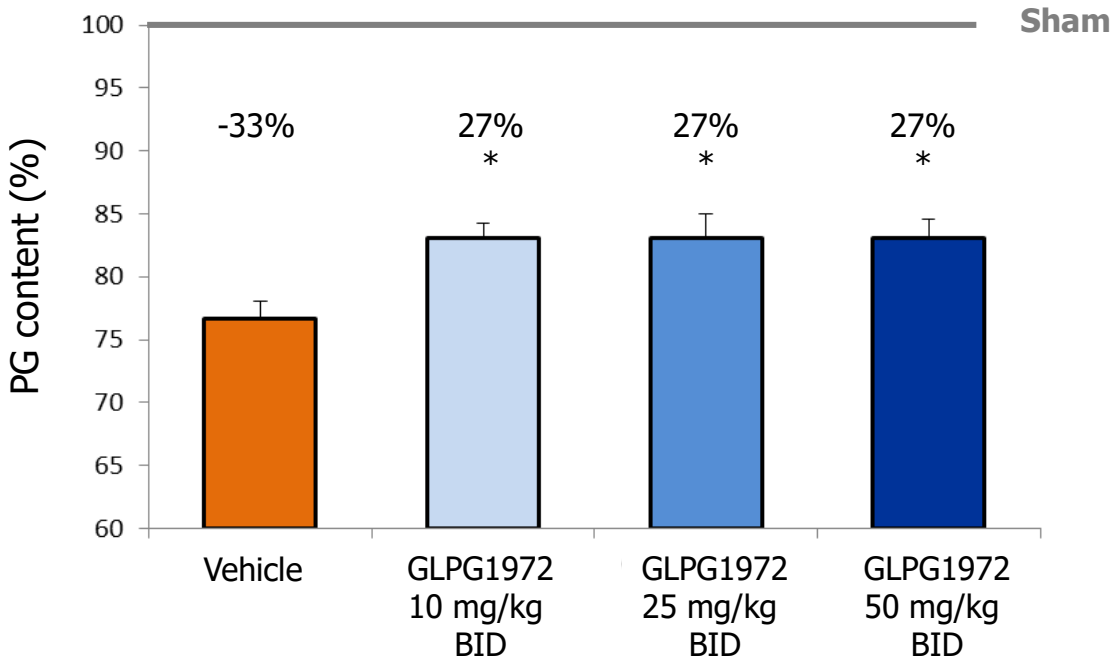
‘1972 reduces OARSI score



Data expressed as mean±sem

Data expressed as median±IQR
Statistics using a stratified Kruskal-Wallis test &
Dunnett multiple comparisons post hoc test
***p<0.001; **p<0.01 vs MNX-vehicle

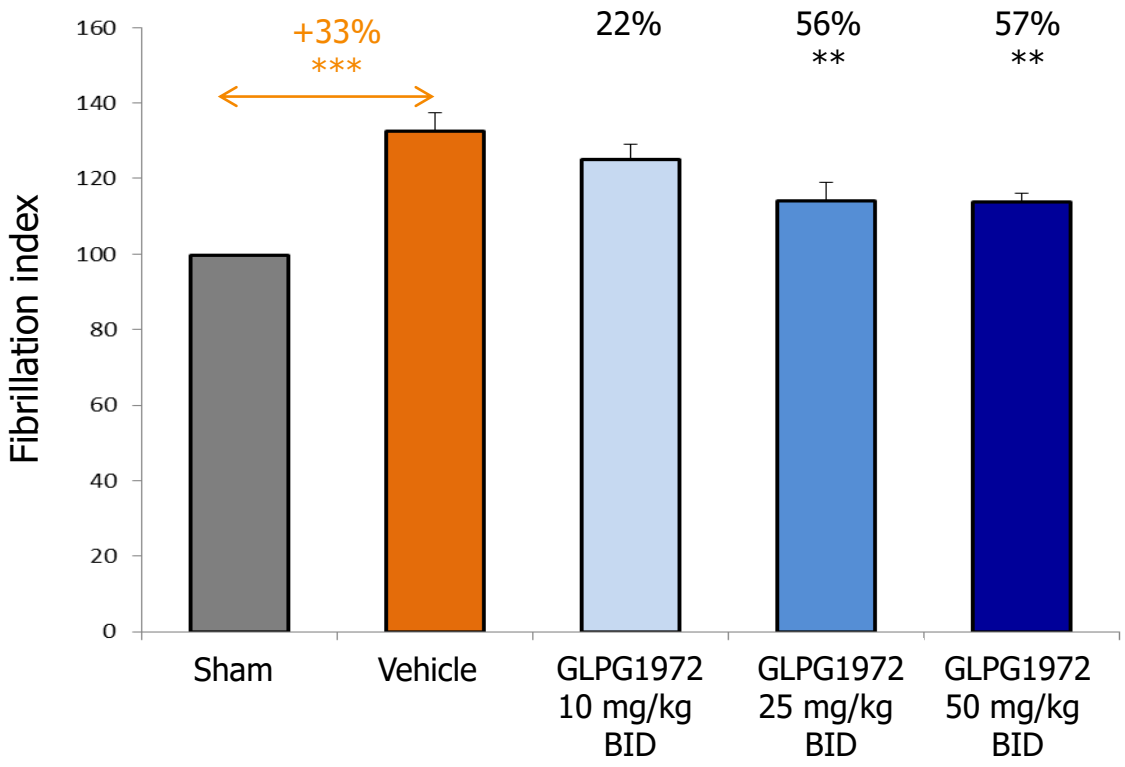
‘1972 preserves proteoglycan content



Data expressed as mean±sem
Anova analysis of variance + Dunnett’s post hoc test:
*p<0.05 versus vehicle

$$\% \text{ Prevention} = \frac{(PG_{\text{Test-group}} - PG_{\text{MNX-group}})}{(PG_{\text{Sham-group}} - PG_{\text{MNX-group}})} \times 100$$

‘1972 reduces fibrillation index



Data expressed as mean±sem
Anova analysis of variance + Dunnett’s post hoc test:
**p<0.01 versus vehicle

$$\% \text{ Prevention} = \frac{(FI_{\text{Test-group}} - FI_{\text{MNX-group}})}{(FI_{\text{Sham-group}} - FI_{\text{MNX-group}})} \times 100$$

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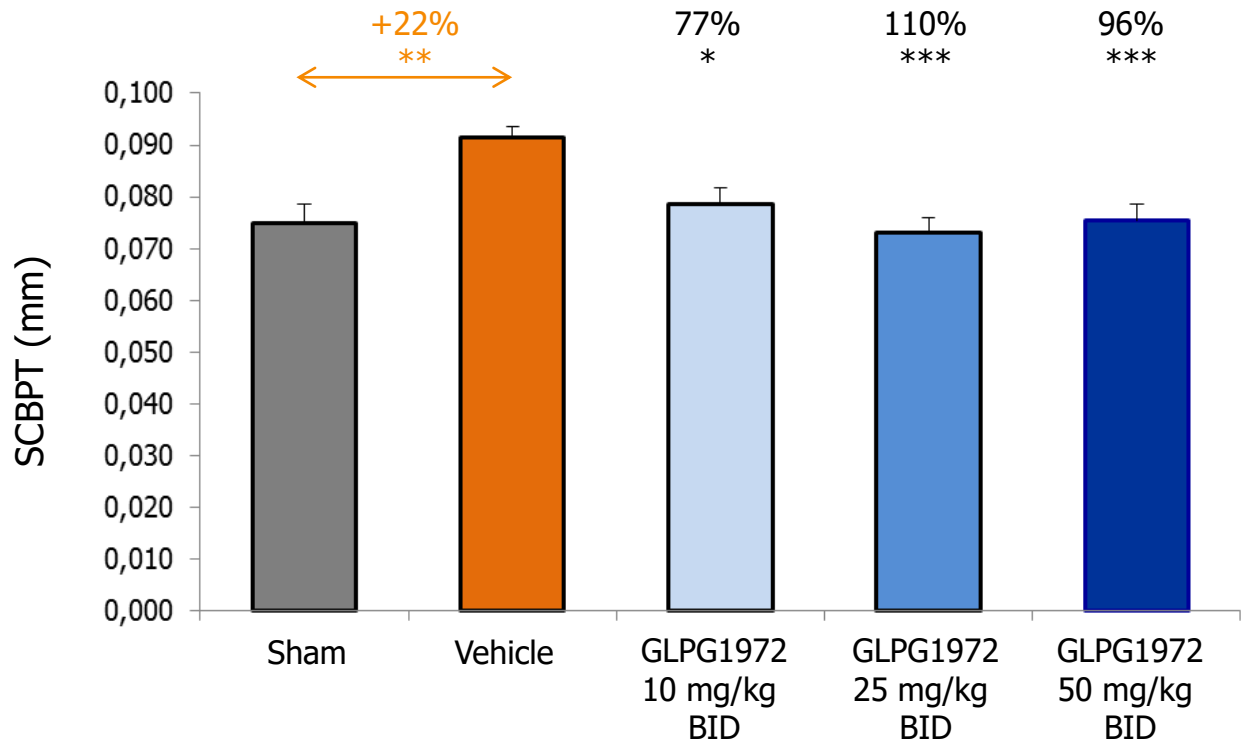
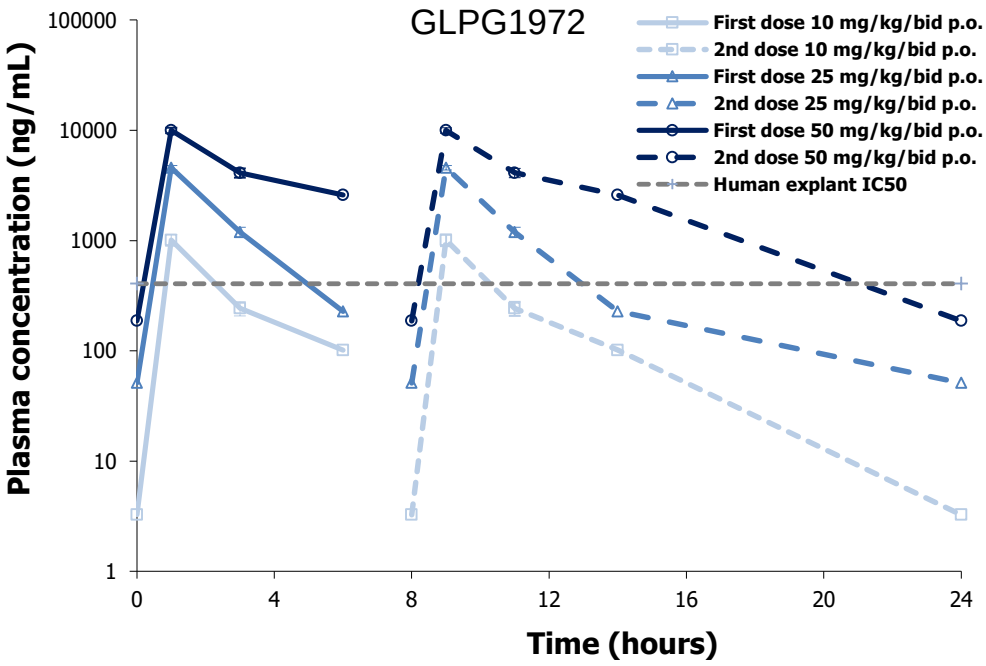
‘1972 prevents subchondral bone plate thickening



Data expressed as mean±sem
Anova analysis of variance + Dunnett’s post hoc test:
*p<0.05, **p<0.01, ***p<0.001 versus vehicle

$$\% \text{ Prevention} = \frac{(SCBPT_{\text{Test-group}} - SCBPT_{\text{MNX-group}})}{(SCBPT_{\text{Sham-group}} - SCBPT_{\text{MNX-group}})} \times 100$$

Steady State PK



Dose (mg/kg BID)	C_{max} (µg/mL)	$AUC_{0\text{-}24h}$ (µg.h/mL)	Cave (ng/mL)	Condyle/ plasma ratio
10	1.01	4.43	185	0.15
25	4.58	19.4	808	0.14
50	9.97	65.6	2,732	0.13

- Multiple rat MNX studies run: MED defined at 18 mg/kg BID
- Average plasma concentration over 24 h was 385 ng/mL

Conclusions

- ‘1972 is an orally bioavailable, potent and-selective ADAMTS-5 inhibitor
- ‘1972 showed a significant DMOAD effect in the rat MNX model: acting on both cartilage and bone pathology
- ‘1972 successful in Ph1 studies (please visit poster # ???)

OA Phase 2 clinical study with ‘1972 to start in 2018

Acknowledgements

Galápagos

- Philippe Clement-Lacroix, Sandrine Meurisse
- Liên Lepescheux, Didier Merciris
- Roland Blanqué, Céline Cottereaux
- Patrick Mollat
- Franck Brebion, Romain Gosmini
- Ellen van der Aar, Monica Borgonovi
- Thierry Christophe, Nele Vandervoort
- Daniel Comas, Pierre Deprez

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- Frédéric De Ceuninck
- Iuliana Botez