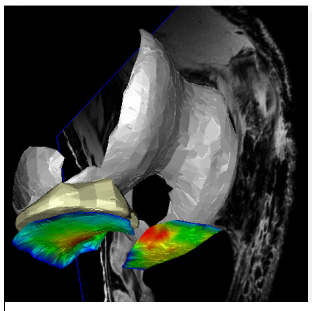

Effect of iNOS Inhibition on Structural Progression of Knee OA Over 2Y –

Defined as MRI-based Quantitative Cartilage Thickness Change

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COI & Funding Source

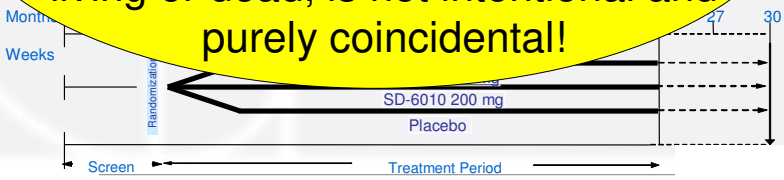
F. Eckstein	Chondrometrics, Pfizer, MerckSerono, Sanofi-Aventis, Abbot, Perceptive, Synthes, Medtronic
R. Buck	StatAnswers Consulting LLC (independent statistical analysis)
W. Wirth	Chondrometrics, MerckSerono,
A. Guermazi	BICL, Novartis, Genzyme, Stryker, MerckSerono, Astra Zeneca
R. Clemmer M.-P. Hellio Le Graverand	Pfizer

sponsored by

Objective

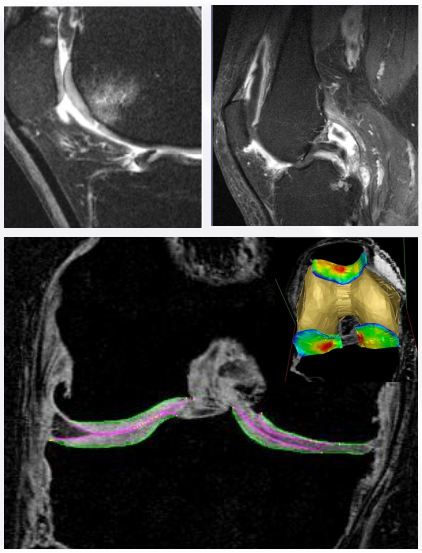
- To evaluate structural (DMOAD) efficacy of 50 /200 mg cindunistat/ SD-6010 (iNOS inhibition) vs. placebo in a A6171016
- Inc

Dislaimer:
The primary endpoint was not met! This analysis is all exploratory and on a „lessons to be learned“ basis. Any resemblance to serious conclusions, y) living or dead, is not intentional and purely coincidental!

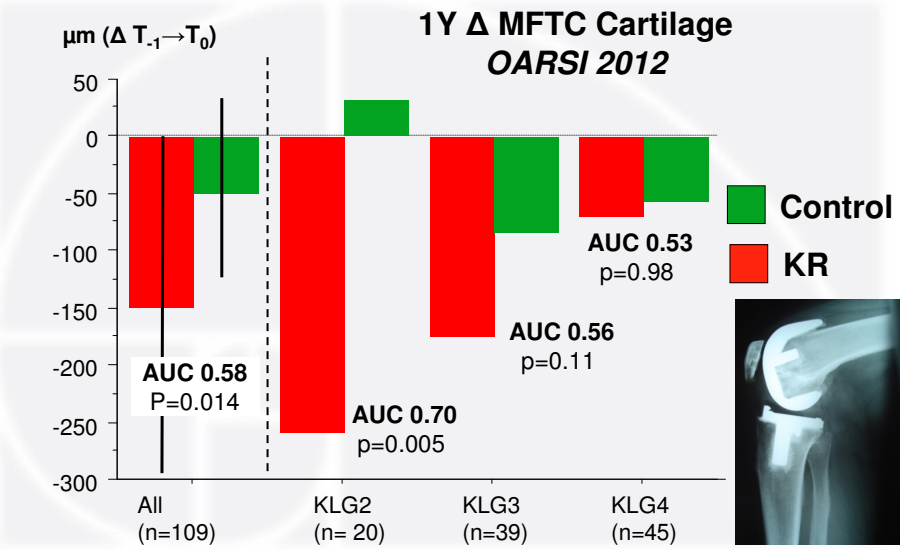


Why MR imaging?

- **Can delineate changes in all synovial tissues**
- **Quantitative measures specific to cartilage loss (physical validation in TKR)**
- **Less prone to positioning issues (tibial alignment)**
- **High precision and sensitivity to change, also in multi-center studies**
  Hudelmaier et al CTO 2010
- **Can provide location-and compartment-independent measures of magnitudes of cartilage thickness change (ordered value [= OV] systems**

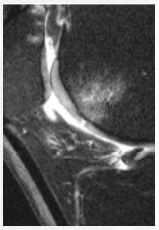


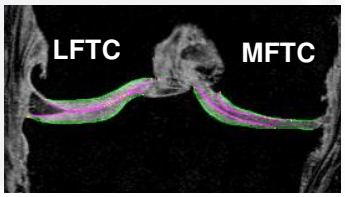
Prediction of Knee Replacement



Patients / Methods

- 66 (of 1457), 62 @ 6M, 47 @ 12M, 34 @ 24M
- SQ evaluation using MOAKS by A.G. (Hunter et al. 2011)
- Coronal 3D FLASH/SPGR we images analyzed by 7 readers (Chondrometrics)
- ThCtAB (change) in 2 compartments, 4 plates, 16 subregions (and 16 OVs of subregions)
- Regression & mixed effect models (R.B.)
  (adjusted for KLG, but not for MC)





Extended Ordered Values

Buck et al. ACR 2009

Wirth et al. O&C 2011

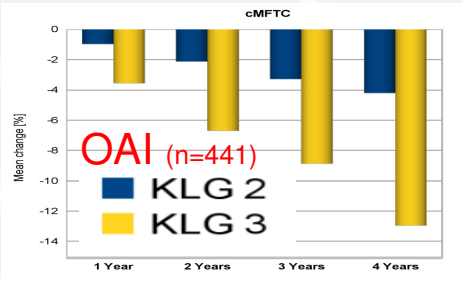
OAI ID	9100262	9474248	9725081
cMT	-0.18	-0.30	-0.12
eMT	-0.25	-0.02	-0.05
iMT	0.08	-0.14	-0.01
aMT	-0.04	0.10	-0.06
pMT	-0.21	-0.01	-0.01
ccMF	-0.85	-0.11	-0.23
ecMF	-0.72	-0.13	-0.15
icMF	-0.06	-0.01	-0.14
cLT	-0.10	-0.62	0.18
eLT	0.04	-0.36	0.00
iLT	-0.12	-0.18	0.11
aLT	-0.04	-0.25	0.17
pLT	0.02	-0.11	-0.34
ccLF	0.01	-0.29	-0.24
ecLF	0.04	-0.38	-0.04
icLF	-0.02	-0.01	-0.12

OV 1

OAI ID	9100262	9474248	9725081
Rank 1	-0.85	-0.62	-0.34
Rank 2	-0.72	-0.36	-0.24
Rank 3	-0.25	-0.36	-0.23
Rank 4	-0.21	-0.30	-0.15
Rank 5	-0.18	-0.29	-0.14
Rank 6	-0.12	-0.25	-0.12
Rank 7	-0.10	-0.18	-0.12
Rank 8	-0.06	-0.14	-0.06
Rank 9	-0.04	-0.13	-0.05
Rank 10	-0.04	-0.11	-0.04
Rank 11	-0.02	-0.11	-0.01
Rank 12	0.01	-0.02	-0.01
Rank 13	0.02	-0.01	0.00
Rank 14	0.04	-0.01	0.11
Rank 15	0.04	0.01	0.17
Rank 16	0.08	0.10	0.18

Results (Demographics)

	Placebo N=25	50mg N=30	200mg N=28	
Age: mn (sd)	60.6 (8.3)	57.9 (8.2)	60.2 (9.5)	=
BMI: mn (sd)	30.7 (3.0)	31.5 (4.2)	31 (4.3)	=
KLG=3: n (%)	9 (36.0%)	18 (60.0%)	17 (60.7%)	≠
Female: n (%)	12 (48%)	23 (76.7%)	15 (53.6%)	≠



A6171016:

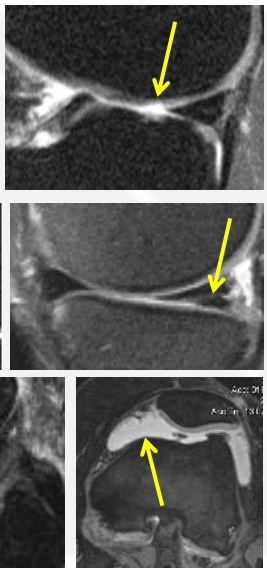
Δ ThC KLG 3 > 2

KLG most important variable explaining variation in ΔThC

Results (MOAKS)

Baseline Prevalence (% patients)

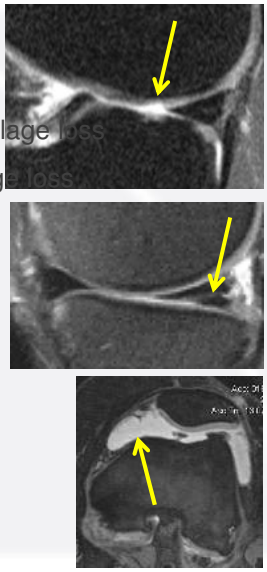
- 98% partial thickness cartilage loss
- 48% full-thickness cartilage loss (dAB)
- 92% BMLs
- 78% menisc. lesions
- 9.3% menisc. hypertr.
- 1.2% menisc. root tear
- 86% menisc. extrusion
- 77% Effusion synovitis
- 64% Hoffa synovitis



Results (MOAKS)

% Patients Δ @ 6/12/24M (max. score)

	6	12	24	months
➢	23	16	32%	Partial thickn. cartilage loss
➢	3	2	12%	Full-thickn. cartilage loss
➢	33	41	51%	BMLs
➢	11	8	15%	Menisc. lesions
➢	1.5	2	2.5%	Menisc. hypertr.
➢	0	0	0%	Menisc. root tear
➢	14	8	12%	Menisc. extrusion
➢	25	27	32%	Effusion synovitis
➢	20	22	10%	Hoffa synovitis



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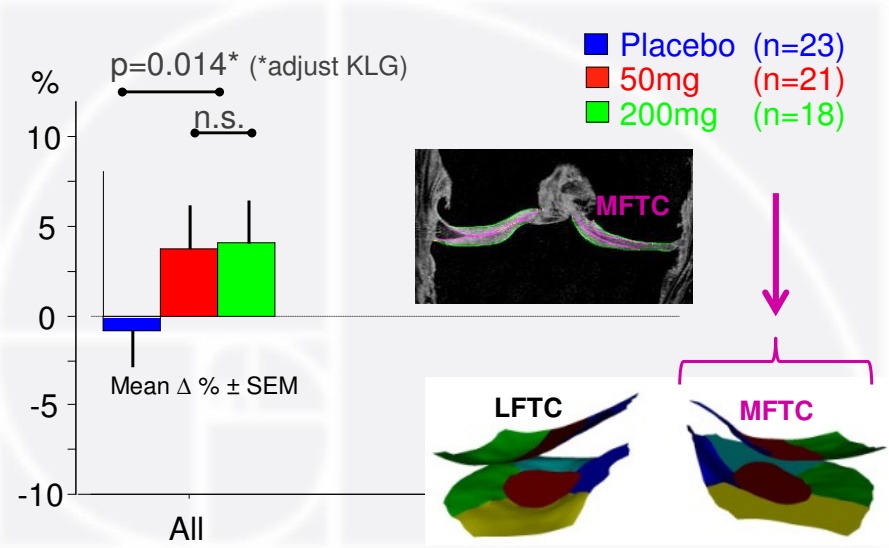
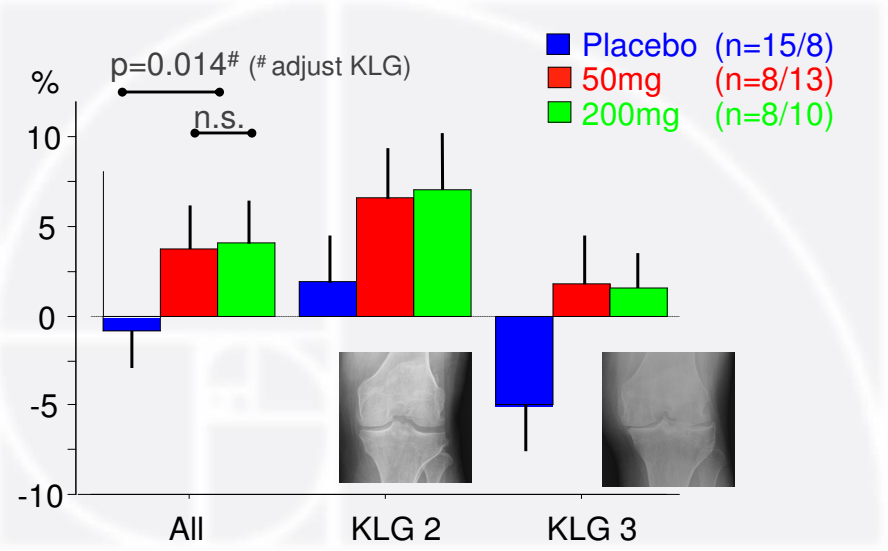
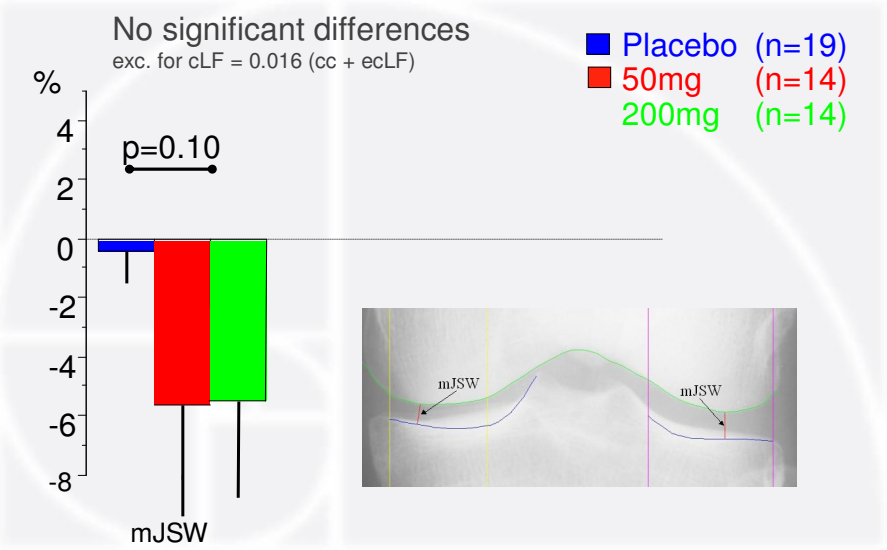
6M ΔThC MFTC (%/y)



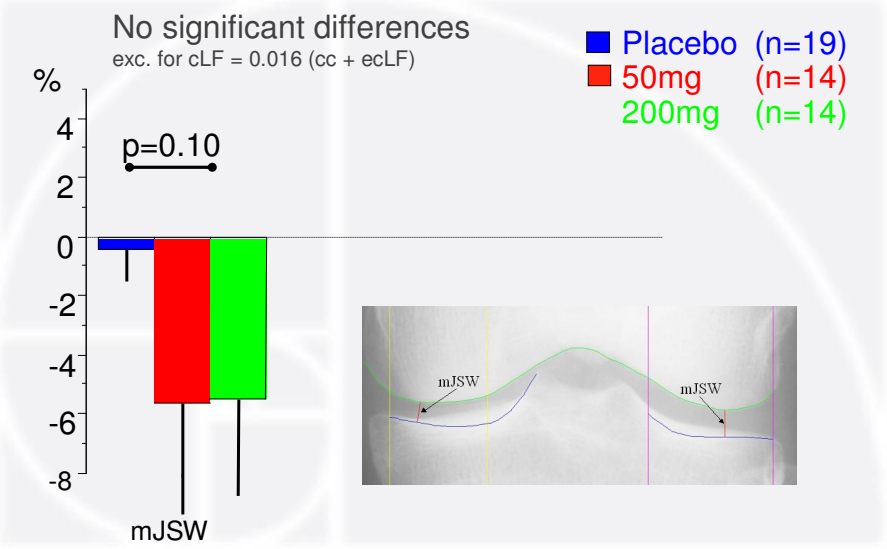
6M ΔThC MFTC (%/y)



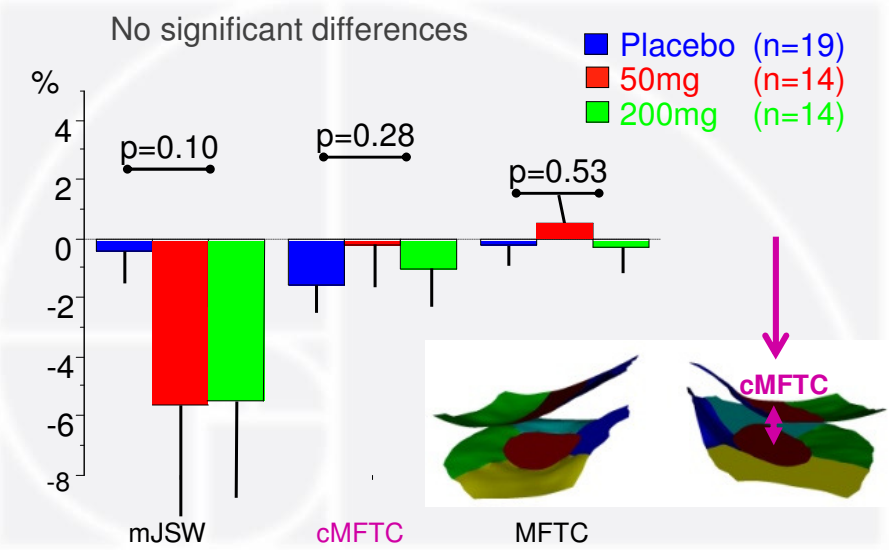
12M Δ mJSW (%/y)



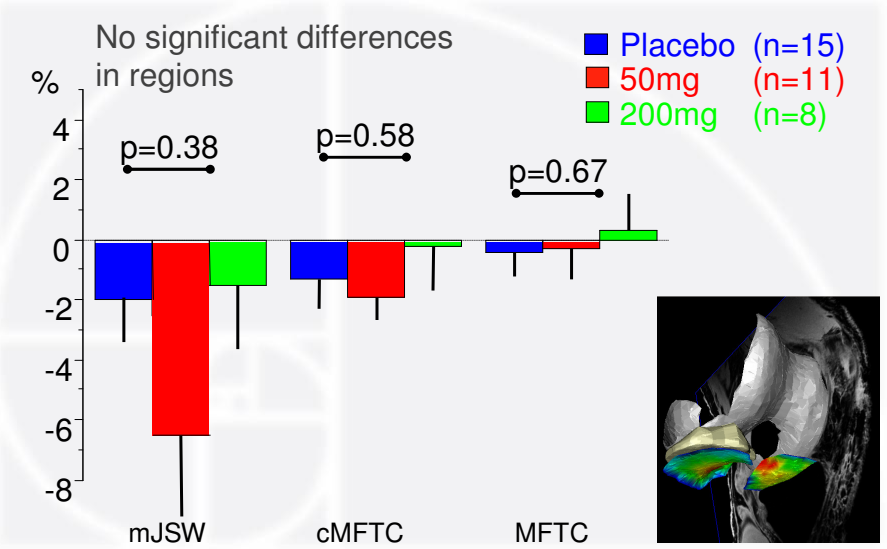
12M Δ mJSW (%/y)



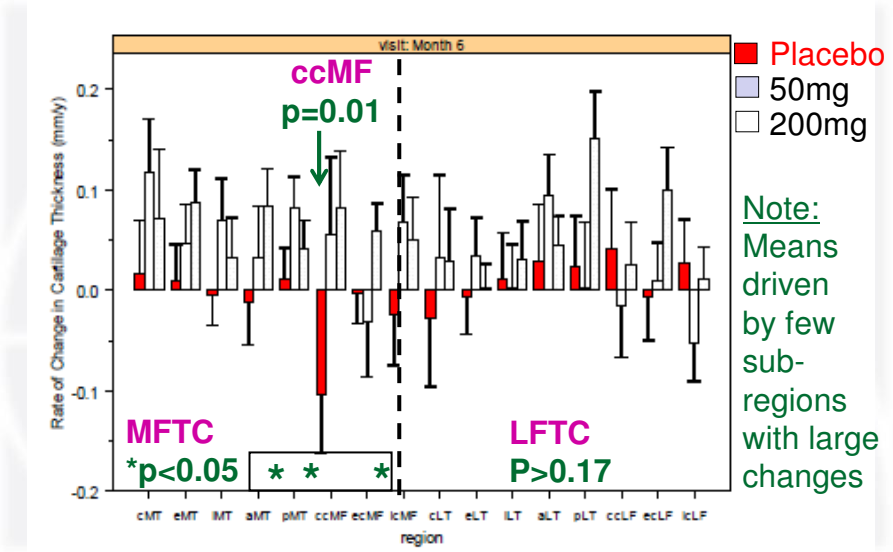
12M ΔThC (c)MFTC (%/y)



24M ΔThC (c)MFTC (%/y)



6M Results (Subregions)



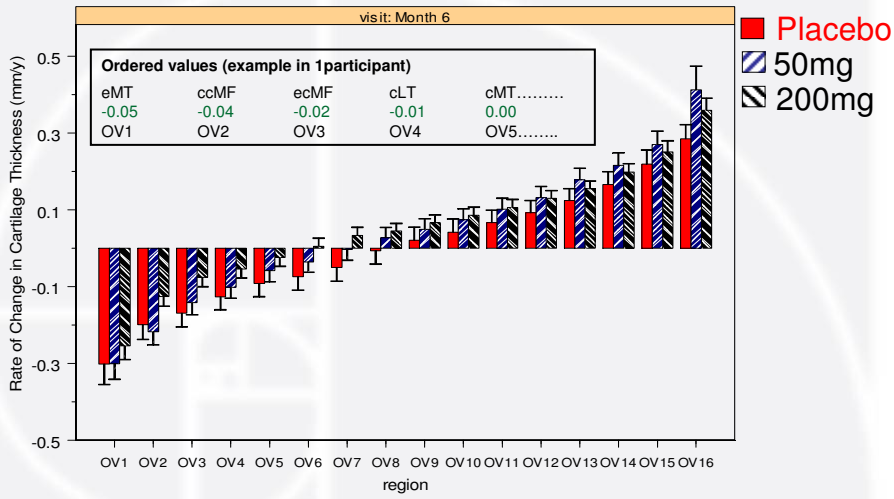
Note: Means driven by few sub-regions with large changes

6-24M Results (Med. Subreg.)

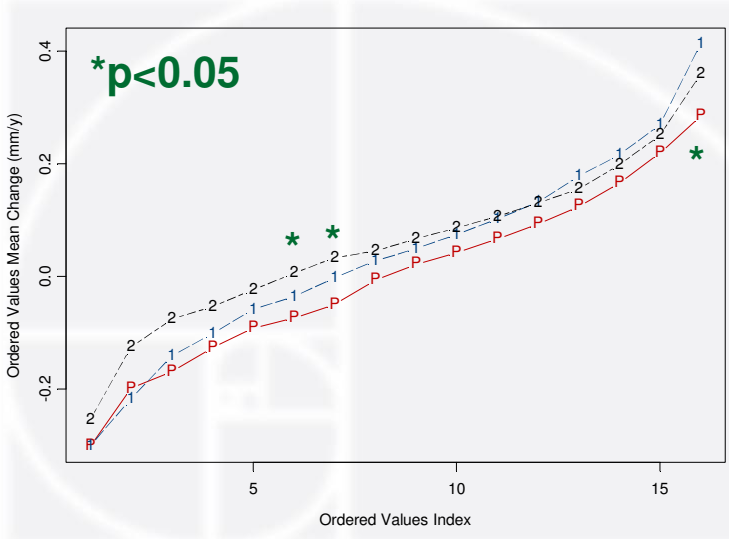
	6M	12M	24M
Placebo n=	24	22	20
% K thinning	21%	32%	47%
% K thickening	25%	37%	40%
50 mg n=	19	15	16
% K thinning	27%	40%	42%
% K thickening	55%	47%	58%
200 mg n=	15	12	9
% K thinning	5%	25%	33%
% K thickening	25%	38%	56%

K=knees (1/subject) in which ≥1 subregion ≠ healthy ref. distribution: proportions not significantly different (Fisher exact test)

6M Results (OVs)



6M Results (OVs)



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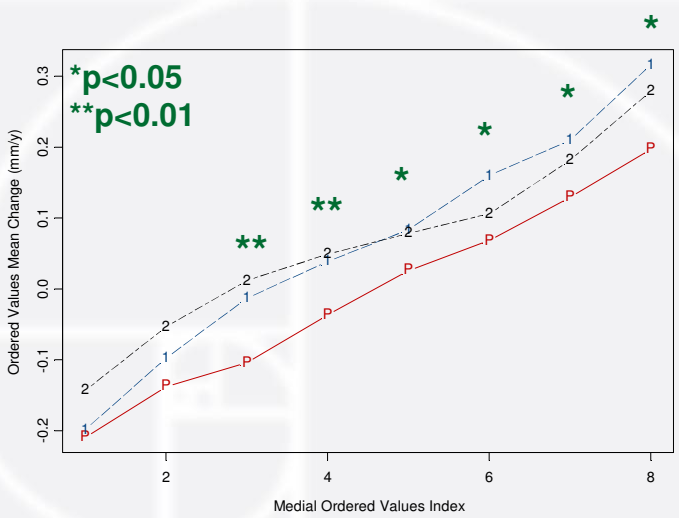
6M Results (Med OVs)



6-24M (mixed effect model)

Drug vs. Placebo	6M (n=62)	12M (n=47)	24M (n=34)
Additive Models			
Med regions	0.33	0.31	0.13
Lat regions	0.99	0.06	0.59
Med OVs	0.005	0.42	0.01
Lat Ovs	0.92	0.43	0.67

Progression Models: see Poster R. Buck et al.

Conclusions

- Small sample sizes and drop out provide challenges in longitudinal studies
- Attempts should be made to obtain equal distributions of KLG2 and KLG3 participants in placebo vs. treatment cohorts
- In knees with medial OA, medial subregions and OVs provide a more sensitive approach to detecting drug effects (vs. plates)
- Models looking at all (medial) subregions or OVs simultaneously are superior
- iNOS inhibition with cindunistat/ SD-6010 may have (at least short term) structural benefits on cartilage status