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***Osteoarthritis and Cartilage*, brief report**

Automated MRI assessment confirms cartilage thickness modification in patients with knee osteoarthritis: post-hoc analysis from a phase II sprifermin study.

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Running headline: Post-hoc analysis of sprifermin study

ABSTRACT

Background: Sprifermin is under investigation as a potential disease-modifying osteoarthritis drug. Previously, 2-year results from the FORWARD study showed significant dose-dependent modification of cartilage thickness in the total femorotibial joint (TFTJ), medial and lateral femorotibial compartments (MFTC, LFTC), and central medial and lateral TFTJ subregions, by quantitative magnetic resonance imaging (qMRI) using manual segmentation.

Objective: To determine whether qMRI findings from FORWARD could be reproduced by an independent method of automated segmentation using an identical dataset and similar anatomical regions in a post-hoc analysis.

Method: Cartilage thickness was assessed at baseline and 6, 12, 18 and 24 months, using automated cartilage segmentation with active appearance models, a supervised machine learning method. Images were blinded for treatment and timepoint. Treatment effect was assessed by observed and adjusted changes using a linear mixed model for repeated measures.

Results: Based on automated segmentation, statistically significant, dose-dependent structural modification of cartilage thickness was observed over 2 years with sprifermin vs placebo for TFTJ (overall treatment effect and dose response, both $P<0.001$), MFTC ($P=0.004$ and $P=0.044$), and LFTC (both $P<0.001$) regions. For highest dose, in the central medial tibial ($P=0.008$), central lateral tibial ($P<0.001$) and central lateral femoral ($P<0.001$) regions.

Conclusions: Cartilage thickness assessed by automated segmentation provided a consistent dose response in structural modification compared with manual segmentation. This is the first time that two independent quantification methods of image analysis have reached the same conclusions in an interventional trial, strengthening the conclusions that sprifermin modifies structural progression in knee osteoarthritis.

Keywords:

Osteoarthritis

DMOAD

Cartilage

Machine learning

Active appearance models

Introduction

Cartilage is a key tissue of interest in structure-modification trials of osteoarthritis (OA). Although radiographic joint space width (JSW), a surrogate for structural progression, is one of the regulatory endpoints in these trials, there is increasing evidence of the benefits of direct measures of cartilage morphology using quantitative magnetic resonance imaging (qMRI)[1]. Techniques employing manual segmentation of cartilage have been explored with respect to a number of morphological characteristics, including volume and thickness. These techniques have been extensively validated, including construct validity against invasive measurement of cartilage volume and thickness, radiographic JSW, predictive and concurrent validity, and clinical outcomes[2].

However, manual segmentation of cartilage morphology is time consuming and challenging, as careful attention must be paid to detecting the eroding outer margin of the cartilage. To address these issues, various methods of semi-automated or fully automated segmentation have been developed. Fully automated methods based on active appearance modeling (AAM) have demonstrated good measurement accuracy for a number of MRI-assessed tissues including knee cartilage[3].

Many previous disease-modifying osteoarthritis drug (DMOAD) studies have focused on use of anticatabolic agents to delay progression of cartilage breakdown[4]. An alternative approach is to stimulate cartilage development and repair. Sprifermin, a novel recombinant human fibroblast growth factor-18, is currently under investigation as a potential DMOAD. Sprifermin induces hyaline cartilage formation in vitro and in vivo by increasing chondrocyte proliferation, resulting in increased overall extracellular matrix production[5, 6].

FORWARD (NCT01919164) is a 5-year, multicenter, randomized, placebo-controlled Phase II study, evaluating the efficacy and safety of intra-articular sprifermin in patients with symptomatic radiographic knee OA. The primary 2-year results from FORWARD showed significant dose-dependent modification of cartilage thickness change in the total femorotibial joint (TFTJ), medial and lateral femorotibial compartments (MFTC, LFTC), and central medial and central lateral TFTJ subregions[7]. Cartilage thickness was measured by qMRI; images were analyzed at a single center by manual cartilage segmentation.

Here, we conducted a retrospective analysis of MR images from FORWARD, to determine whether qMRI findings assessed by manual segmentation could be reproduced using a previously validated independent method of automated segmentation[3].

Methods

Patients aged 40–85 years with symptomatic radiographic knee OA, Kellgren-Lawrence Grade 2 or 3, and medial JSW ≥2.5 mm in the target knee were randomized (1:1:1:1:1) to receive double-blinded 3-weekly intra-articular injections of sprifermin 100 µg every 6 months (q6mo); 100 µg every 12 months (q12mo); 30 µg q6mo; 30 µg q12mo; or placebo. MR images were acquired at baseline, 6, 12, 18 and 24 months using 1.5 or 3 Tesla clinical MRI scanners using a coronal spoiled gradient echo sequence with fat saturation or water excitation, and 1.5 mm slice width with 0.31 mm x 0.31 mm in-plane resolution, as previously reported[7]. The study protocol was approved by independent ethics committees or institutional review boards at all study sites. Written informed consent was obtained from all

participants, and the study was performed in accordance with the ethical principles of the Declaration of Helsinki.

The manual segmentation method has been presented previously[2, 7, 8]. As with the original analysis[7], all images were blinded with regard to acquisition order and active treatment/placebo status.

Automated cartilage segmentation was performed as a retrospective analysis using a previously validated method[3]. AAM, a supervised machine learning method (Imorphics Ltd, Manchester, UK), was used to produce maps of cartilage thickness for femoral and tibial cartilage surfaces[3]. Each timepoint was analyzed independently. As for the previously-employed manual method, total cartilage thickness was computed as total volume divided by total surface area (i.e., average cartilage thickness) for the TFTJ, MFTC and LFTC regions. These regions replicated those used for manual segmentation by Chondrometrics by following published region descriptions[8, 9] (**Supplementary Figure 1**) and were automatically projected out to each image segmentation during image search by the AAM.

In addition, regions representing the central medial tibial (cMT), central medial femoral (cMF), central lateral tibial (cLT) and central lateral femoral (cLF) plates were produced according to previously described manual definition on the mean bone shape[10]. These central regions are similar, but not identical to the segmentation regions previously used in the FORWARD trial (**Supplementary Figure 1**)[7, 8]. Again, these regions were automatically projected out to each image segmentation during image search by the AAM. The cMT, cMF, cLT and cLF regions were defined by Imorphics based on independent data from the Osteoarthritis Initiative and were based on regions that changed most in an Osteoarthritis Initiative data set[11]. Dense pointwise maps of cartilage changes were produced as standardized response means (SRMs) of change over 2 years in all available knees. The central regions corresponding to SRM >0.7 were defined by smoothing with an enclosing ellipsoid shape (cLT and cMT) or rectangle (cMF and cLF). Of note, these regions correspond closely to the meniscal windows of the joint at 15° of flexion. Average cartilage thickness in these regions was calculated by taking the mean of a set of thickness measures orthogonal to the bone surface and located at each of the AAM correspondence landmarks.

As in the previous analyses[7], the treatment effect on change from baseline was assessed for each method by observed and adjusted changes using a linear mixed model for repeated measures. The analysis was implemented in SAS (PROC MIXED) using treatment group, time, and pooled country as class variables, baseline as covariate, and treatment by time interaction. An unstructured covariance matrix was used to account for the repeated measures within each patient. The linear dose relationship was tested at Year 2 at the two-sided 5% significance level. If the null hypothesis of no linear relation was rejected, the effect of treatment was assessed by pairwise comparisons of absolute change from baseline in cartilage thickness (sprifermin treatment groups versus placebo). Dunnett's approach was used to account for comparison of four dose groups to placebo at a given timepoint. No direct statistical comparisons between the manual and automated methods were prespecified or conducted, as this was not the aim of the study. Statistical significance was set at $P < 0.05$.

Results

550 patients were recruited at 12 sites in the EU, USA and Hong Kong, and 549 were randomized as an intention to treat (ITT) set. The modified ITT (mITT) analysis set included all patients from the ITT analysis set who had a baseline (prior to first injection) and at least one post-treatment qMRI assessment

available up to Year 2. mITT subject numbers were 101 (100 µg q6mo); 99 (100 µg q12mo); 99 (30 µg q6mo); 99 (30 µg q12mo); and 96 (placebo).

Using the automated method, statistically significant, dose-dependent structural modification of cartilage thickness was observed over 2 years with sprifermin vs placebo for the TFTJ region (**Figure 1, top panel**) (overall treatment effect and dose response across all doses, both $P < 0.001$), and also for the MFTC ($P = 0.004$ and $P = 0.044$) and LFTC (both $P < 0.001$) regions. Statistically significant, dose-dependent structural modification of cartilage thickness over 2 years was also observed for sprifermin vs placebo in the cMT (100 µg q6mo [$P = 0.008$]), cLT (100 µg q6mo, q12mo [both $P < 0.001$]) and cLF (100 µg q6mo, q12mo [both $P < 0.001$]) regions. In the cMF region, there was no significant treatment effect ($P = 0.149$), but there was a linear trend for dose responsiveness ($P = 0.013$).

Statistically significant differences in the mean change from baseline in cartilage thickness at Year 2 for the highest sprifermin dose (100 µg q6mo) vs placebo were obtained for the TFTJ, MFTC and LFTC regions for both methods (**Table 1**). Statistically significant differences were observed from baseline for the highest sprifermin dose vs placebo in the cMT, cLT and cLF regions using the automated method:

- cMT (mean difference [95% confidence interval (CI)]: 0.09 [0.02, 0.16], $P = 0.008$)
- cMF (linear trend: $P = 0.013$; mean difference [95% CI]: 0.06 [0.00, 0.12], $P = 0.061$)
- cLT (mean difference [95% CI]: 0.15 [0.08, 0.22], $P < 0.001$)
- cLF (mean difference [95% CI]: 0.10 [0.06, 0.13], $P < 0.001$)

Scatter plots and regression lines showed consistency of results between the manual and automated methods of MR image analysis assessing change in cartilage thickness from baseline to 2 years in the TFTJ, MFTJ and LFTJ regions (**Supplementary Figure 2**).

Discussion

Measures of cartilage morphometry have been utilized previously in DMOAD trials[7]. However, this is the first time that two independent methods of image analysis have been applied to the same interventional trial population and have reached the same conclusions regarding structural modification, demonstrating beneficial effects of sprifermin on cartilage thickness.[1]

Careful manual segmentation and review by an expert reader is the gold standard for morphometric analysis of cartilage using MR images[12]. MRI cartilage thickness measures are associated with OA progression and joint replacement and provide more responsive measures of progression than radiographic JSW[13-17]. Automated methods of cartilage segmentation based on machine learning and artificial intelligence are showing increasing promise[12]. Here we used a previously published method based on AAMs to provide independent comparator measurements. Although this automated method has been shown to be highly correlated with manual segmentation, Bland-Altman analysis of agreement does indicate systematic bias, and in measurement of longitudinal change, the automated method produced almost twice the cartilage thickness change of the manual method[3]. This, and the fact that correlation may vary depending on the datasets that are compared, means that some differences in measurements would be expected between the automated and manual methods applied to this image dataset.

This automated method produced a consistent and similar pattern of structural modification in the FORWARD study compared with previously reported manual segmentation (**Figure 1**)[7]. Although a larger change in the mean cartilage thickness from baseline was observed for all dose groups, as noted previously[3], it was associated with greater measurement variance compared to the manual method. It should be noted that the average cartilage thickness loss that was seen in this study (around 30 µm over two years) is much less than one voxel width. Cartilage loss is therefore a change in the margin of cartilage that is defined by the partial volume in an MR image sampling voxel, which is typically 5–10 times the magnitude of the change over 2 years. It is likely that the human operator and the automated algorithm make different decisions about where the cartilage edge actually lies within the image, and this may explain the differences in cartilage thickness changes and measurement error seen here.

There were some limitations in this study. There was no direct comparison of methods, as this was not the aim of the study. Further, this was a post-hoc analysis; however, all the available image data were utilized even though some may not have been optimal for automated analysis. Although the TFTJ, MFTJ and LFTJ regions used for the previous manual segmentation analysis were replicated for the automated analysis, the cMT, cLT, cMF and cLF regions were not used originally, but rather aggregate measures of medial and lateral femorotibial subregions (cMFTC and cLFTC, respectively) were used, and therefore these subregion results could not be compared directly.

In summary, this post-hoc analysis is unique in that two independent quantitative image analysis methods demonstrated the same results, and strengthens the conclusions that the investigational agent, sprifermin, modifies cartilage loss/structural progression in knee OA.

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Author contributions

FM, HG and CL were responsible for the conception and design of the study. AB was responsible for drafting the article. AB, PC, MB and FE provided critical revision of the article for important intellectual content. FM provided statistical expertise. All authors were responsible for analysis and interpretation of the data and for final approval of the article and take responsibility for the integrity of the work.

Role of the funding source

This study is sponsored by Merck KGaA, Darmstadt, Germany. The study sponsor was involved in the study design, collection, analysis, and interpretation of data and in the writing of the manuscript and decision to submit for publication.

Conflict of interest

AB and **MB** are employees of Imorphics, Manchester, UK. **PGC** has done consultancies or speakers bureaus for AbbVie, Bristol Myers Squibb, EMD Serono, Flexion Therapeutics, Galapagos, GlaxoSmithKline, Novartis, Pfizer and Stryker. **CL** and **HG** are employees of Merck KGaA, Darmstadt, Germany. **FM** is an employee of EMD Serono (a business of Merck KGaA, Darmstadt, Germany). **FE** is an employee and shareholder of Chondrometrics GmbH, and has received consulting fees from Merck KGaA, Samumed LLC, Abbvie, Bioclinica, TissueGene, Servier, Galapagos, Roche, and Novartis

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Figures

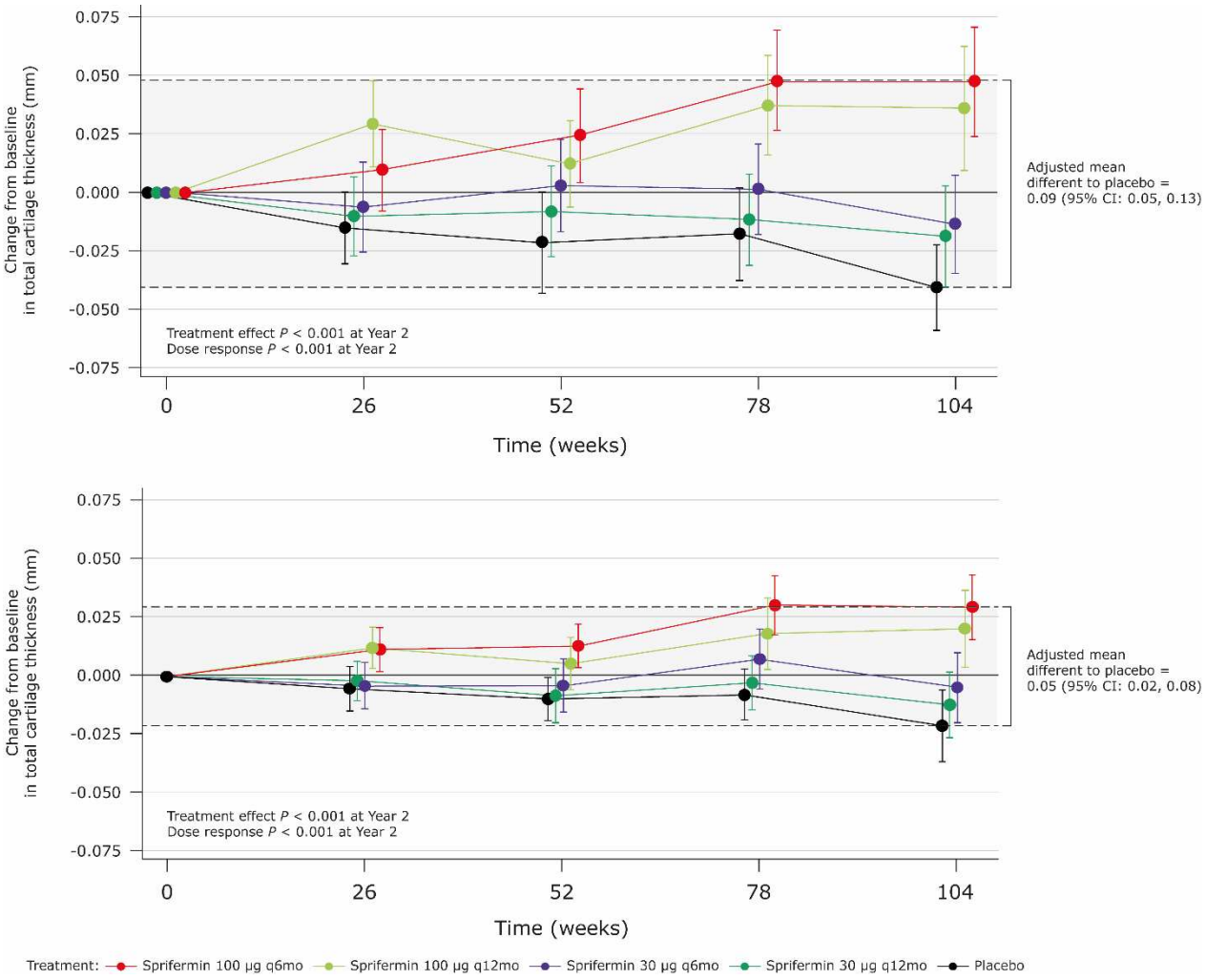


Fig. 1. Cartilage thickness in the total femorotibial joint determined by automated segmentation (top) and manual segmentation (bottom)

CI, confidence interval; q6mo, every 6 months; q12mo, every 12 months.

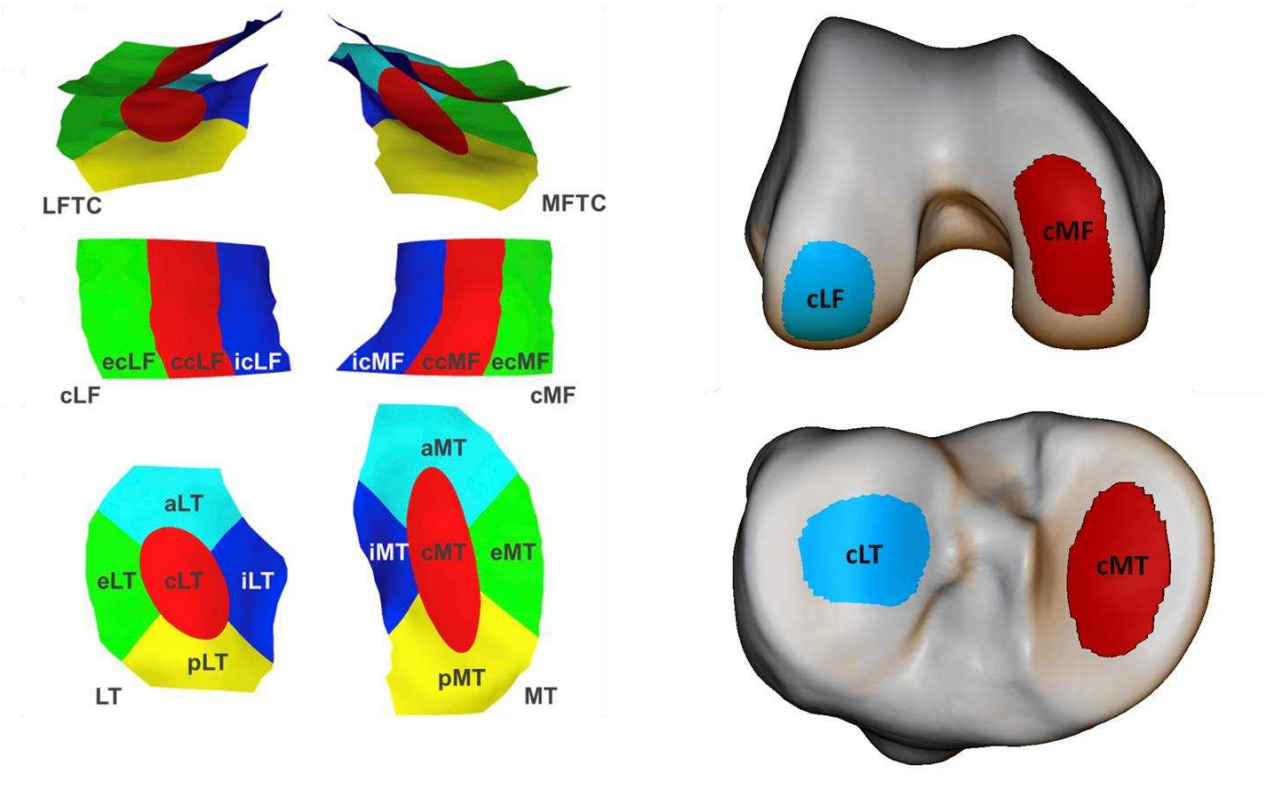
Table 1

Change from baseline at Year 2 in cartilage thickness (mm) using automated segmentation and manual segmentation – mITT

	Automated segmentation				Manual segmentation[7]			
	Sprifermin 100 µg q6mo (*n* = 101)	Placebo (*n* = 96)	Sprifermin 100 µg q6mo vs placebo		Sprifermin 100 µg q6mo (*n* = 101)	Placebo (*n* = 96)	Sprifermin 100 µg q6mo vs placebo	
Region	Observed mean (SD) change from baseline, mm		Adjusted mean difference (95% CI)[a]	*P*-value	Observed mean (SD) change from baseline, mm		Adjusted mean difference (95% CI)[a]	*P*-value
TFTJ	0.05 (0.11)	-0.04 (0.08)	0.09 (0.05, 0.13)	< 0.001	0.03 (0.07)	-0.02 (0.07)	0.05 (0.02, 0.08)	< 0.001
MFTC	0.03 (0.15)	-0.04 (0.14)	0.07 (0.01, 0.12)	0.011	0.02 (0.08)	-0.03 (0.12)	0.05 (0.01, 0.08)	0.003
LFTC	0.07 (0.12)	-0.04 (0.10)	0.11 (0.07, 0.15)	< 0.001	0.04 (0.06)	-0.01 (0.05)	0.05 (0.03, 0.08)	< 0.001

[a]Adjusted using ANCOVA on change from baseline, including treatment group, timepoint, and (pooled) country as fixed factors, baseline value as covariate, and treatment by timepoint as interaction.
CI, confidence interval; LFTC, lateral femorotibial compartment; MFTC, medial femorotibial compartment; SD, standard deviation; TFTJ, total femorotibial joint.

Supplementary Figure 1



Supplementary Fig. 1. Regions of interest defined for manual segmentation and automated segmentation (left panel) and additional regions for automated segmentation (right panel)

aLT, anterior lateral tibial; aMT, anterior medial tibial; cLF, central lateral femoral; ccLF, central subregion of the central lateral femoral; cLT, central lateral tibial; ccMF, central subregion of the central medial femoral; cMF, central medial femoral; cMT, central medial tibial; ecLF, external subregion of the central lateral femoral; ecMF, external subregion of the central medial femoral; eLT, external lateral tibial; eMT, external medial tibial; icLF, internal subregion of the central lateral femoral; icMF, internal subregion of the central medial femoral; iLT, internal lateral tibial; iMT, internal medial tibial; LFTC, lateral femorotibial compartment; LT, lateral tibial; MFTC, medial femorotibial compartment; MT, medial tibial; pLT, posterior lateral tibial; pMT, posterior medial tibial

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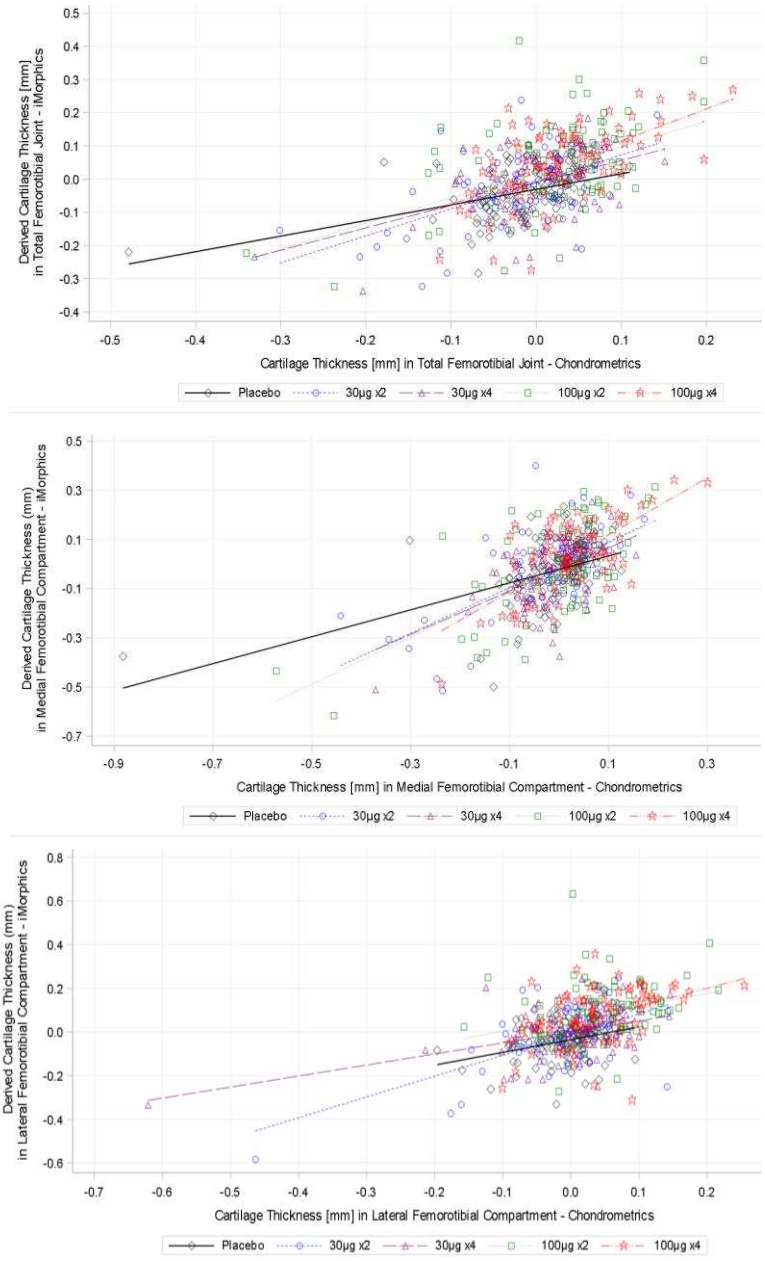
Supplementary Figure 2



Supplementary Fig. 2. Scatter plot and regression lines for change from baseline at Year 2 of cartilage thickness in the total femorotibial joint (top), medial femorotibial joint (middle) and lateral femorotibial joint (bottom): manual vs automated segmentation