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Patterns of decline and evidence of subgroups in patients with Alzheimer's disease taking galantamine for up to 48 months

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SUMMARY

Background Lacking long-term placebo-controlled trials of cholinesterase inhibitors (ChEIs) in Alzheimer's disease, how decline is modeled is crucial to interpreting the effects of long-term, open-label use. We aimed to: 1) understand changes in cognition and function in people taking galantamine; (2) identify treatment subgroups.

Methods This is an open-label long-term extension (up to 48 months) of two placebo-controlled clinical trials from Europe and Canada. At baseline, 240 patients with mild-moderate Alzheimer's disease at baseline had received galantamine continuously for 36 months. The trajectory of scores on the Alzheimer's Disease Assessment Scale—Cognitive Subscale (ADAS-Cog) and the Disability Assessment for Dementia (DAD) was modeled over 48 months. Goodness of fit was compared using normalized residuals and by calculating correlation coefficients between observed and fitted data. Iterative K-means clustering identified subgroups.

Results Of 240 patients, 51 (21%) withdrew between months 36–48 (nine died and 12 with adverse events). The mean ADAS-Cog worsened from 22.6 (mean) $\pm$ 8.6 (SD) at baseline to 31.3 $\pm$ 3.1, with similar changes in the DAD. The logistic function fit better (ADAS-Cog norm of residuals = 2.05, $r = 0.993$; DAD = 2.21, $r = 0.998$) than the commonly used Stern equation (ADAS-Cog = 4.22, $r = 0.944$; DAD = 7.51, $r = 0.986$). K-means clustering identified three stable groups; least decline ($n = 82$), persistent progression ($n = 75$), and an intermediate group ($n = 82$). Initial conditions were important: the mean ADAS-Cog score for those with least decline was 15 $\pm$ 8, better than both the intermediate group (20 $\pm$ 9) and persistent progressors (30 $\pm$ 10; $p < 0.001$).

Conclusions Alzheimer's disease patients show variable long-term decline that is best modeled as a logistic function, not as linear decline. Over 48 months, about one-third of patients showed little decline, while one-third showed important decline.

KEY WORDS — Alzheimer's disease; galantamine; long term treatment; responders; effect sizes

INTRODUCTION

Alzheimer's disease usually progresses relentlessly. Cholinesterase inhibition can give dose-responsive, clinically detectable effect up to 12 months, (Rockwood, 2004) but longer-term effects are not clear. Even though stability or slowing are desired, (Doody *et al*., 2001; Lyketsos *et al*., 2004; Raskind *et al*., 2004; Bullock and Dengiz, 2005; Farlow and Lilly, 2005) for most treated patients, dementia progresses (Birks, 2006).

Continued disease progression motivates skepticism about whether treatment is meaningful (Scheider, 2004; Ritchie *et al*., 2004; Kaduszkiewicz *et al*., 2005). The longest placebo-controlled trial showed no impact

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of donepezil on institutionalization, although it showed significant long-term cognitive and functional benefit (Courtney *et al*., 2004). Still, the trial's multiple washout design and high loss to follow-up limit generalizability. Without more double-blind data, we must rely on open label studies, which are subject to cohort effects, survivor bias and modeling assumptions (Cummings, 2006). Typically, clinical trials data are extrapolated (Pirttilä *et al*., 2004; Feldman *et al*., 2005) using the 'Stern equation' (Stern *et al*., 1994). Untangling treatment benefit is challenging. Drop-out and survivor bias favour patients with little decline. Even some untreated patients stabilize (Bowler *et al*., 1998; Johnsen *et al*., 2000; Perrault *et al*., 2002; Holmes and Lovestone, 2003). Regression to the mean can occur (i.e. patients who initially respond are later more likely to decline) (Courtney *et al*., 2004). Moreover, neither a linear relationship between time and disease, nor uniformity of response should be assumed (Chan and Holford, 2001).

Instead of simple extrapolation, other analytical techniques can be employed (Johnsen *et al*., 2000). Here we examine 48 month outcomes in patients from the pivotal European-Canadian trials of galantamine. We modeled patterns of decline, and evaluated whether stable patient subgroups (cf. regression to the mean) could be detected. This is an investigator-initiated secondary analysis of the database extended from the reported of Pirttilä and colleagues (2004).

METHODS

Subjects

Patients had already received up to 36 months of galantamine treatment (Pirttilä *et al*., 2004) (Figure 1) from double-blind trials (Rockwood *et al*., 2001; Wilcock *et al*., 2000). Extension study enrollment required patients to remain in good health, provide written informed consent and take no other anti-dementia medication. Patients were excluded if they had developed other clinically significant conditions, including psychiatric, neurologic or cerebrovascular disease. Study conduct accorded with the 'Declaration of Helsinki', and the protocol was reviewed by an independent Institutional Review Board.

Design

This open-label, extension study included centers from Australia, Canada, South Africa and seven Nordic/European countries. The initial visit of this trial was to take place within 1 month of the patient's final visit in the preceding open-label study. There was no randomization or blinding. All patients received a single 12-mg tablet of galantamine twice daily. Adverse events and vital signs were evaluated at 6-month intervals, and safety and efficacy assessments were performed at study end.

Outcome measures

The 11-item, 70-point cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog/11) was used to assess efficacy at visits 1 and 3/final visit. Higher scores indicate greater impairment. The 100-point Disability Assessment for Dementia (DAD) was used to assess personal and instrumental activities of daily living; higher scores indicates better functioning.

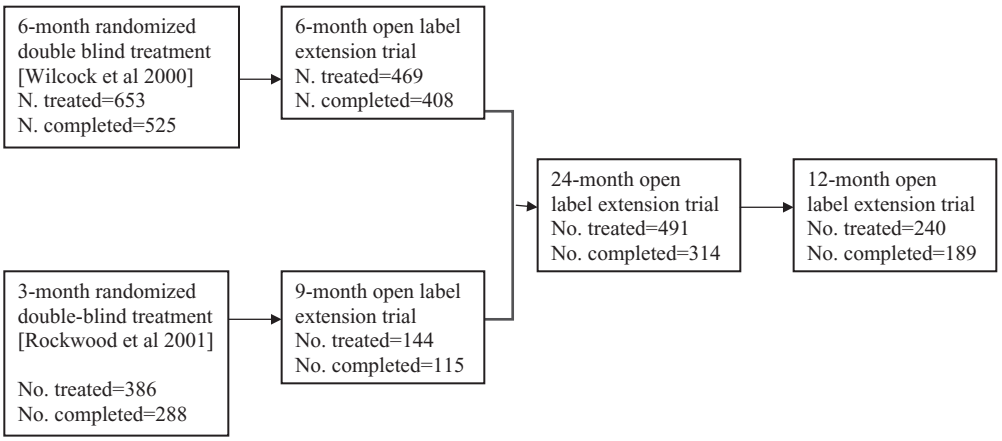

Figure 1. Trial sequence for the use of galantamine over 48 months.

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Analysis.

To classify the extent of disease progression, we first evaluated absolute changes, based on ADAS-Cog/11 cut-points of 0-point or fewer increase, 4-point or fewer increase, 7-point or fewer increase, 10-point or fewer increase, and 20-point or fewer increase (Raskind *et al*., 2004). As did Raskind *et al*., we compared slopes of patients who completed with those of patients who discontinued, thereby allowing an evaluation of differential drop-out as an explanation of the response profile. (Raskind *et al*., 2004). To evaluate change in the DAD score, we noted that 12-month longitudinal data from 504 placebo-treated AD patients, the linear annual rate of change in score was 11 on the DAD scale, (Aerssens *et al*., 2001) and that an open-label extension trial of galantamine in vascular/mixed dementia, the average 12-month change months was a 7.4 point decline (Erkinjuntti *et al*., 2003). We therefore defined levels as 0-point or less decrease, 4-point or more decrease, 7-point or more decrease, 11-point or more decrease, and 20 + point decrease

Analyses were carried out using MatLab 7.1 software (MatWorks Inc.). Linear (using the Stern equation) (Stern *et al*., 1994) and logistic fits were applied to the mean ADAS-cog and DAD scores. Parameters of the logistic function, scaled so that $y = 1/(1 + a\exp(bx))$ were found using a least-squares nonlinear fitting procedure. Goodness of fit was evaluated by comparing the norm of residuals between the observational data and the curve, and by comparing differences in the norms of residuals between the models using Fisher's test. In addition, we calculated the correlation coefficients between observed mean values of each score and those fitted by each model, and compared between models using Fisher's 'r-to-z' transformation (z-test) (Zar, 1984).

As the opportunity to change by a particular amount can itself change over the distribution of the initial test scores, another way to understand stabilization is to portray the distribution of the absolute test scores over time. For comparison with standard portrayals, we also present changes in mean scores over the 48-month interval; within-group differences in scores over time were compared using ANOVA with Tukey post hoc analysis of comparisons between time-points. Mean subgroup scores were compared over time using a mixed effects model.

We used a data-driven approach to operationalize slowing. The *K*-means cluster analysis iteratively uses non-supervised learning algorithms to identify groups-here, patients with distinctive changes in cognition. (Bishop, 1995; MacKay, 2003). Using SPSS 12.0 for Windows, we assigned $K = 3$ centers to represent clustering of N points ($n = 240$). The points are iteratively adjusted so that each of the N points is assigned to one of the K clusters, and each of the K clusters is the mean of its assigned points. We chose three clusters to evaluate the clinical experience that some patients do well, some badly and another group in between. By comparing their baseline scores, we are able to evaluate characteristics that might be associated with the three clusters, signified by the ability to remain in the trial with the least amount of decline, relative to the starting group.

RESULTS

Of the 314 patients who completed the preceding 36-month follow-up, 240 entered this final 12-month study after 36 months on treatment; of these 185 (77%) completed 48 months (Figure 1). One patient, who did not have documented dosing information, was excluded. Most patients were women, and about 75 years old, with cognitive and functional impairment consistent with the mild-moderate stage of dementia (Table 1).

Safety

Fifty-one patients withdrew; 12 had adverse events, of which two were falls, but no other occurred more than once. A fall was recorded in one other patient, who did not withdraw. Eight other adverse events occurred in 10% or more of patents (Table 2). Seven percent of adverse events were rated as 'severe' including falls (5%), pathological fractures (5%), aggressive reactions (4.4%), cerebrovascular disorder (4.4%), injuries (4.4%), and pneumonia (4.4).

Cognition and function

The mean ADAS-Cog worsened from 22.6 ± 8.6 at baseline to 31.3 ± 13.1 at 48 months (Figure 2). Similarly, the DAD declined from 73.4 ± 18.1 to 36.1 ± 29.0. Goodness of fit for the Stern equation, measured by the norm of residuals, was 4.22 ($r = 0.944$) for the ADAS-Cog and 7.51 ($r = 0.986$) for the DAD, compared with, for the logistic function, 2.05 ($r = 0.993$; $p < 0.05$ compared with the linear fit) for the ADAS-Cog and 2.21($r = 0.998$; $p < 0.05$ compared with the linear fit) for the DAD.

The fit can be interpreted as follows. There are two parameters: *a* depends on the initial (baseline) status; *b* characterizes the rate of change. The time independent

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Table 1. Baseline characteristics, according to dose at the end of the placebo phase

Characteristic	Patients			
	All	GAL up to 12 mg	GAL 16 mg	Placebo
	($n = 239$)	($n = 98$)	($n = 65$)	($n = 76$)
N (%) Female	145 (60.7)	56 (57.1)	40 (61.5)	49 (64.5)
Age (y)(SD)	74.7 (8.3)	73.5 (8.3)	73.2 (9.5)	76.8 (6.5)
DAD Mean (SD)	73 (18.1)	76.1 (16.7)	72.8 (20.0)	70.3 (19.9)
MMSE Mean (SD)	20.0 (3.4)	20.4 (3.5)	19.8 (3.5)	19.6 (3.5)
ADAS-Cog/11 (SD)	22.6 (8.6)	23.1 (9.2)	21.6 (7.8)	22.8 (8.2)

Table 2. Adverse events occurring in 10% or more of patients receiving open-label glantamine*

Adverse Event	All patients	Initially galantamine treated patients
	($n = 239$)	($n = 163$)
Agitation	48 (20)	31 (19)
Insomnia	38 (16)	29 (18)
Urinary incontinence	35 (15)	20 (12)
Depression	31 (13)	18 (11)
Constipation	30 (13)	17 (10)
Fall	28 (12)	15 (9)
Urinary tract infection	27 (11)	9 (5)
Aggressive reaction	25 (10)	16 (10)
Injury	23 (10)	18 (11)

*Data are given as number (percentage) of each group.

parameter a equals 40 for both measures, while the rate b is 0.14/month for function and 0.19/month for cognition. Note, however, that the b parameter estimate is not informative clinically, as the process is not linear. Instead, we need to consider the ratio $ln(a)/b$, which tells us where change is maximal. This occurs at 25 months for functional decline and at 19 months for cognitive decline. Patients who withdrew from the study declined faster in both function ($p < 0.01$) and cognition ($p < 0.01$) (Figure 3).

The *K*-means analysis confirmed three clusters of patients, each initially stable, after which one cluster ($n = 82$) had the lowest rate of progression, another had persistent progression (Cluster 3, $n = 75$) and a third was intermediate (Cluster 2, $n = 82$) (Figure 4). Initial conditions were important—e.g. there were significant differences in the baseline MMSE and ADAS-cog ($p < 0.01$). Patients with the least progression started with the highest cognitive function (Table 3) which was stable for 24 months. The intermediate group was stable for about 12 months, whereas the group with persistent decline was stable for about only 6 months. By contrast, the DAD was relatively stability for all groups for about 12 months, after which decline was similar in shape, but from a higher starting point amongst those with the most stable course (Figure 4).

DISCUSSION

Patients with mild-moderate Alzheimer's disease who were able to stay on galantamine for up to 48 months showed three profiles of cognitive and functional

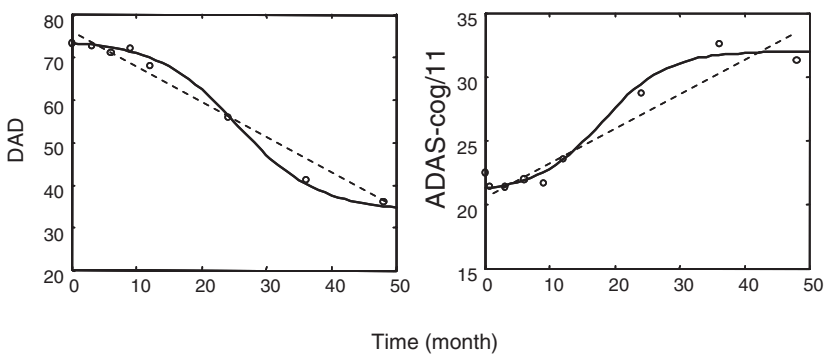

Figure 2. Time trajectories of mean changes in cognition (right) and function (left) over 48 months. Circles correspond to the observed data. The dashed lines show the fit assuming linear decline; the solid line is the fit assuming a logistic function.

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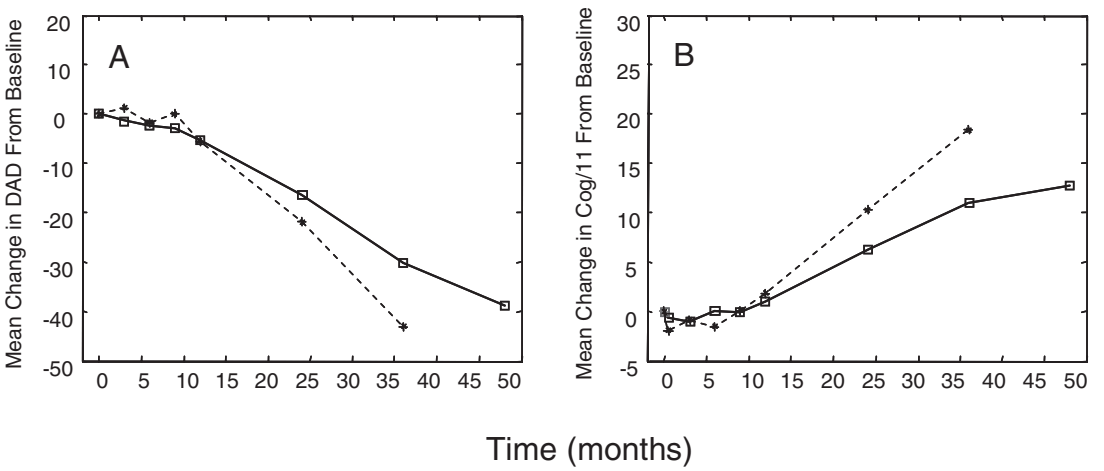

Figure 3. Functional (A) and cognitive decline (B) in drop-out patients vs. the rest of the participants. Dashed lines show the average trajectories of DAD (A) and ADAS-Cog (B) in drop-out patients, solid lines show the average trajectories of the rest of the participants.

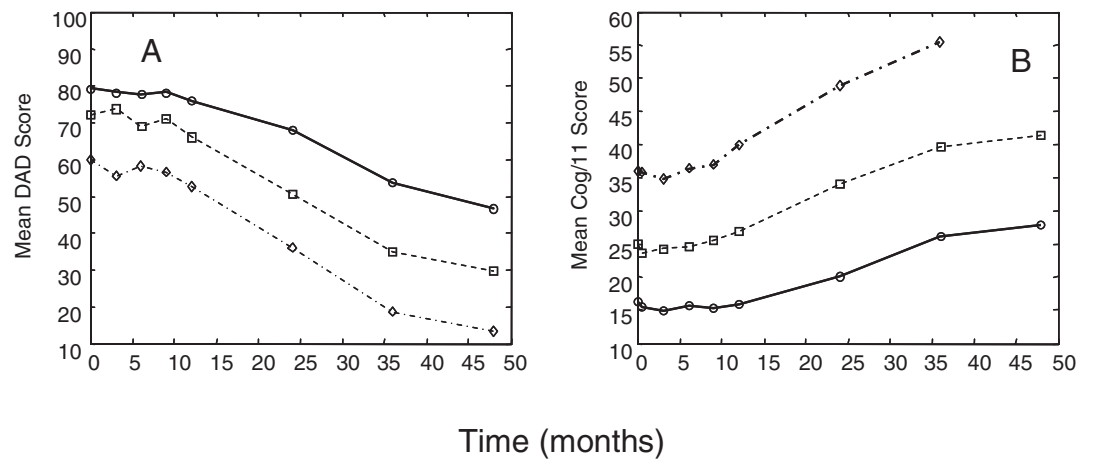

Figure 4. The DAD data (panel A) and the ADAS-Cog data (panel B). The three lines correspond to averages within each group of the trajectories of functional and cognitive decline. Note that three sub-groups are clearly different by the initial values of DAD (A) and ADAS-Cog (B).

Table 3. Characteristics of disease progression groups, at baseline grouped by ADAS-Cog strata

Characteristic	Cluster 1 ($n = 82$) stable	Cluster 2 ($n = 82$) intermediate	Cluster 3 ($n = 75$) progression
Mean age (SD)	75.3 (7.6)	73.6 (9.6)	74.5 (7.6)
% Females	55.4	53.7	74.7
Mean MMSE (SD)	22.2 (1.8)	20.5 (2.9)	17.0 (3.3)
Mean DAD (SD)	76.7 (15.2)	77.4 (15.8)	65.1 (20.7)
Mean ADAS-Cog/11 (SD)	16.1 (5.2)	20.8 (4.4)	31.9 (7.2)
% who initially took placebo	31.3	29.3	34.7
% discontinued after 36 months	10.8	23.2	26.7

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progression: very little, quite marked, and in between. Decline was non-linear. Patients with the least initial impairment showed the least decline. Patients who discontinued tended to have declined more than those stayed on treatment.

Our data must be interpreted with caution. We had no placebo control group. Generalizability is limited, as patients who start trials and those who stay in them are not likely to represent patients in practice. The study also has strengths. We have re-evaluated how best to model decline and demonstrated that a logistic model gives a better fit than does a widely used linear model, especially after 24 months. Modeling decline as non-linear accords with earlier observations (Morris *et al*., 1993; Stern *et al*., 1994; Mitnitski *et al*., 1999). Although claims have been made for linear decline (including that non-linearity might be a statistical artifact (Suh *et al*., 2004)) the shape of the decline changed over time, so that, especially after 24 months non-linearity was evident. Even better for analyzing long-term effects would be 'retrieved drop-out' (RDO) analysis, in which patients who withdraw from the trial are reassessed at the specified endpoint. This, however, was not available to us.

Interestingly, the proportions conform to the common clinical observation of 'one-third /one-third/one-third', for groups with only slow decline, or no evident response, or somewhere in between. Note that while the *K*-means algorithm is sensitive to the choice of the number of clusters, there is no reason that choosing three clusters should have yielded distinguishable groups, nor that these groups should split in thirds. These groupings were present even though, in general, those who withdrew did worse than those who remained on treatment.

The definition of long-term treatment response is controversial. Still, despite the inherent uncertainty, physicians must say something to patients about whether long-term treatment might have merit, and this must be said knowing not just that a placebo control group is not available, but that it is unlikely to become available. The AD2000 trial had only a handful of patients in double-blind conditions by 4 years, making the prospect of generalizable data from long-term trials unrealistic, even if ethical. Comparison with historical controls is problematic, so other possibilities should be considered.

Drop-out bias seems an incomplete explanation of who stays in trials, as even amongst people who stay on long-term treatment, varying degrees of progression can be found. Still, the course of patients in the three groups was largely stable, so that the regression to the mean hypothesis, particularly advanced by the AD2000 authors, was not evident here. Rather we found that people with the least decline by 48 months had generally had the least decline throughout the study.

Patients with the least decline started with the best cognitive scores. While to treatment advocates this might suggest initiating therapy as soon as possible, skeptics might suggest that it simply means that some people with Alzheimer's disease have slow progression. Here, both the ADAS-Cog and DAD analyses identify a small proportion of people with little decline, so the matter appears not be one of instrumentation. Note that while for most patients Alzheimer's disease is relentlessly progressive, it is not uniformly so. Between 15–22% of patients show only slow decline (Johnsen *et al*., 2003; Perrault *et al*., 2002; Holmes and Lovestone, 2003) but why they do is not well understood. If it is important to know not just from where an individual patient starts, but also how they got there, future studies might profit by attempting to estimate the rapidity of decline prior to treatment. Of note, we found no significant ($p > 0.5$) long-term differences by initial treatment assignment as either galantamine or placebo. There are, however, evident differences up to about 9 months.

Our data also contribute to the debate on the best means to identify responders. The ADAS-Cog includes little about executive function, compared with the DAD, and thus is less likely to be responsive to improved executive function (or slowed decline) which often helps define a successful treatment response (Rockwood *et al*., 2004; Behl *et al*., 2006). While how response is defined seems to dictate how often it is detected (van Dyck *et al*., 2006) the existence of subgroups seems likely by any measure.

The evaluation of long-term treatment effects is complex, and can benefit from better modeling, which here showed what clinicians have observed: that some patients do better than others. The potential importance of initial conditions particularly requires further study, and is motivating further inquiries by our group.

CONFLICT OF INTEREST AND DISCLOSURE STATEMENT

Kenneth Rockwood has received speaking and ad hoc consulting fees and research grants from Janssen-Ortho and from Shire, which license galantamine and consulting fees from Pfizer, Novartis, Lundbeck and Glaxo Smith Kline, which make or are developing competing compounds.

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KEY POINTS

- Over 48 months of treatment with galantamine, decline in cognition and function was not linear.
- Three groups of patients could be identified: those with the least progression in cognition and function, those with the most progression, and an intermediate group.
- The patterns merged after an initial period of stability, which was about 12 months for function.
- Cognition was stable for the group with least decline for 24 months, but only for 6 months for the group with the most decline.
- Patients with the least impairment at baseline had the least degree of progression.

ROLE OF THE SPONSORS

This was an investigator-initiated analysis. No sponsor had any role in these analyses. Specifically, while Janssen Ortho provided the data and partial funding, and reviewed the analysis for accuracy, it made no suggestion about how the analyses should be carried out or presented. Janssen Ortho saw a penultimate version of the manuscript prior to submission, with the final version submitted to the journal by the authors, and copies sent to Janssen-Ortho.

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