EXTENDED REPORT

The first double-blind, randomised, parallel-group certolizumab pegol study in methotrexate-naive early rheumatoid arthritis patients with poor prognostic factors, C-OPERA, shows inhibition of radiographic progression

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ABSTRACT

Objectives To evaluate efficacy and safety of combination therapy using certolizumab pegol (CZP) and methotrexate (MTX) as first-line treatment for MTX-naive, early rheumatoid arthritis (RA) with poor prognostic factors, compared with MTX alone.

Methods MTX-naive, early RA patients with ≤12 months persistent disease, high anti-cyclic citrullinated peptide, and either rheumatoid factor positive and/or presence of bone erosions were enrolled in this multicentre, double-blind, randomised placebo (PBO)-controlled study. Patients were randomised 1:1 to CZP+MTX or PBO+MTX for 52 weeks. Primary endpoint was inhibition of radiographic progression (change from baseline in modified Total Sharp Score (mTSS CFB)) at week 52. Secondary endpoints were mTSS CFB at week 24, and clinical remission rates at weeks 24 and 52.

Results 316 patients randomised to CZP+MTX (n=159) or PBO+MTX (n=157) had comparable baseline characteristics reflecting features of early RA (mean disease duration: 4.0 vs 4.3 months; Disease Activity Score 28-joint assessment (DAS28)): 5.4 vs 5.5; mTSS: 5.2 vs 6.0). CZP+MTX group showed significantly greater inhibition of radiographic progression relative to PBO+MTX at week 52 (mTSS CFB=0.36 vs 1.58; p<0.001) and week 24 (mTSS CFB=0.26 vs 0.86; p=0.003). Clinical remission rates (Simple Disease Activity Index, Boolean and DAS28 (ESR)) of the CZP+MTX group were significantly higher compared with those of the PBO+MTX group, at weeks 24 and 52. Safety results in both groups were similar, with no new safety signals observed with addition of CZP to MTX.

Conclusions In MTX-naive early RA patients with poor prognostic factors, CZP+MTX significantly inhibited structural damage and reduced RA signs and symptoms, demonstrating the efficacy of CZP in these patients.

Trial registration number (NCT01451203).

INTRODUCTION

The emergence of biological agents targeting inflammatory cytokines such as tumour necrosis factor (TNF), which play key roles in the pathogenesis of rheumatoid arthritis (RA), has been of great importance. The effectiveness of these agents at inhibiting joint damage progression, in addition to providing symptom relief, has brought a paradigm shift to RA treatment. Since joint damage progression is rarely reversible, earlier treatment with effective drugs would be relevant in clinical practice.

Treatment guidelines and recommendations published by the European League Against Rheumatism (EULAR), the American College of Rheumatology (ACR) and the Japan College of Rheumatology recommend that all patients with RA should be treated with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) from the point of diagnosis. Methotrexate (MTX), either as monotherapy or in combination with other csDMARDs, should be given first-line unless contraindicated. For patients at risk of rapid disease progression, addition of a biologic can be considered if treatment targets are not achieved using csDMARDs alone. Earlier recognition of RA has become possible for many patients by application of the 2010 ACR/EULAR classification criteria. Ultimately, early diagnosis and intervention with effective therapeutics maximises the chance of preventing joint damage progression in order to maintain quality of life.

Certolizumab pegol (CZP) is a humanised anti-TNF antibody fragment conjugated to polyethylene glycol, approved for treatment of inflammatory diseases, including RA. Efficacy and safety of CZP in established RA has been demonstrated in several studies but is previously unreported in MTX-naive early RA.

Herein, we conducted the Certolizumab–Optimal Prevention of joint damage for Early RA (C-OPERA) study, designed to include MTX-naive, early RA patients with poor prognostic factors. The study was double-blind (DB) for 1 year, with either CZP or placebo (PBO) administered concomitantly with MTX. Following this, the trial was open label...
for another year, whereby completers of the DB period were maintained on MTX monotherapy after discontinuing CZP. This report comprises results from the 1-year DB period.

METHODS

Patients

Eligible patients were 20–64 years old with RA fulfilling the 2010 ACR/EULAR classification criteria. Patients had ≤12 months of persistent arthritic symptoms, at least moderate disease activity (Disease Activity Score 28-joint assessment (DAS28) with erythrocyte sedimentation rate (ESR) ≥3.2) and were MTX-naive. In addition, patients had poor prognostic factors: high anti-cyclic citrullinated peptide (anti-CCP) antibody (≥3× upper limit of normal (ULN)) and either positive rheumatoid factor (RF) and/or presence of bone erosions (based on radiographs of hands/feet, assessed by the investigator at each study site). Patients with high risk of infection (current use of antibiotics, history of serious/chronic infection treated by antibiotics within 6 months) or history of/active tuberculosis or malignancy, and patients previously exposed to MTX, leflunomide or biological DMARDs were excluded.

Study design

C-OPERA, a phase III multicentre study (NCT01451203), was DB and PBO-controlled to week 52, with a subsequent 52-week follow-up period when patients received MTX monotherapy. Patients were randomised 1:1 to either CZP+MTX or PBO+MTX (MTX monotherapy) via an interactive web-response system. Drug administration was performed by dedicated non-blinded persons due to distinguishability of CZP from PBO; however, these personnel were not permitted to engage in other study activities to maintain blinding. All investigators and healthcare professionals involved in safety/efficacy assessments were blind to study medications. Study drugs were subcutaneously administered as a loading dose of CZP 400 mg or PBO at weeks 0, 2 and 4, followed by CZP 200 mg or PBO every two weeks from week 6 to week 50. Oral MTX (8 mg/week) was initiated simultaneously. MTX dose was increased to 12 mg/week at week 4, 16 mg/week at week 8 and maintained at 16 mg/week thereafter. As per protocol, dose escalation of MTX could be postponed only for safety concerns or due to adverse events (AEs), in which case the dose was maintained at the highest tolerable dose. Patients who did not achieve an improvement of symptoms at or after week 24, that is, if moderate or higher disease activity (DAS28 (ESR) ≥3.2) persisted ≥4 weeks, in either treatment arm, were eligible to receive rescue treatment with open-label CZP after discontinuing DB period. Co-administration of any DMARD except MTX was prohibited during the study.

The study was conducted from October 2011 to August 2013 at 73 sites in Japan after approval by the Institutional Review Board designated by each site, in compliance with ethical principles of the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent.

Efficacy assessments

The primary efficacy endpoint was inhibition of joint damage progression, assessed as change from baseline (CFB) in van der
Heijde modified Total Sharp Score (mTSS) at week 52. The same measure at week 24 was a secondary efficacy endpoint. mTSS was evaluated by two independent readers in accordance with previously reported methods. In addition to mTSS CFB, non-progression (defined: mTSS CFB ≤0.5) and the rapid radiographic progression rate (RRP; defined: yearly progression (YP) ≥3) were analysed. Other secondary efficacy endpoints included clinical remission rates, assessed by ACR/EULAR criteria (Simple Disease Activity Index (SDAI)-based and Boolean-based) and DAS28 (ESR) at weeks 24 and 52.

Signs and symptoms were assessed by clinical remission rates (SDAI, Boolean and DAS28 (ESR)), functional remission rates (Health Assessment Questionnaire Disability Index (HAQ-DI)) and ACR20/50/70 responses, evaluated at each time point.

### Safety assessments
All undesirable events during the DB period were recorded as AEs or serious AEs. Safety was evaluated by laboratory tests (haematological, blood chemistry, urinalysis), chest radiographs and ECGs.

### Statistical analyses
Sample size was based on expected difference in mTSS CFB at week 52 between CZP and PBO groups of 2.57±6.75. Verification of superiority of CZP+MTX over MTX monotherapy for primary endpoint would then have 90% power at a two-sided significance level of p=0.05 with 146 patients per group (thus the planned number was 150 patients).

Primary analyses used the full analysis set, defined as patients who received ≥1 dose of study drug and provided any efficacy data thereafter. For the imputation of missing data, linear extrapolation was used for mTSS and last observation carried forward used for other efficacy variables. Non-responder imputation was added as a sensitivity analysis for clinical remission analyses. For the primary endpoint, an analysis of covariance (ANCOVA) model was used for mTSS CFB by converting measured values to rank scores and using treatment group as a factor and baseline rank score as a covariate. Fisher’s exact test was used for analyses of non-progression, RRP in mTSS, clinical remission and ACR20/50/70 response.

### RESULTS
Patient baseline demographics/characteristics
Of 319 patients randomised, 316 (159, CZP+MTX; 157, PBO +MTX) received study drug. Of these, 111 patients (69.8%) in the CZP+MTX group and 73 patients (46.5%) in the PBO +MTX group completed the 52-week DB period (figure 1). Fewer PBO +MTX patients completed DB period than CZP +MTX patients, mainly due to the increased number of discontinuations (figure 1).

Treatment groups were generally balanced with respect to demographic and baseline characteristics (table 1). Overall, patients’ mean age was 49 years (range 21–64 years). Mean RA duration (time from onset of persistent arthritic symptoms) was approximately 4 months in both groups. All patients had high titre (≥2 times ULN) anti-CCP antibody; approximately 95% were RF positive. Bone erosion was confirmed in 50% of patients. Mean±SD DAS28 (ESR) was 5.4±1.1 for CZP+MTX and 5.5±1.2 for PBO+MTX. Mean (median) mTSS in CZP+MTX and PBO+MTX was 5.2 (1.3) and 6.0 (1.3), and no radiographic damage (mTSS ≤0.5) was observed in 35.2% and 35.7% of patients, respectively. There was no difference between groups in mean baseline body weight (57.4±11.3 in CZP+MTX, 57.4±10.6 in PBO+MTX; kg, mean±SD) or average weekly MTX dose throughout the study period (11.6±3.0 in CZP+MTX, 11.6±2.7 in PBO+MTX; mg/week).

### Inhibition of joint damage progression
For the primary endpoint, mTSS CFB (mean±SD) at week 52 was 0.36±2.70 with CZP+MTX and 1.58±4.86 with PBO +MTX, statistically significant by ANCOVA on the ranks (p=0.001). At week 24, smaller mTSS CFB was observed with CZP+MTX compared with PBO+MTX (0.26±1.55 vs 0.86±2.37; p=0.003) (figure 2A).

The percentage of patients with non-progression (mTSS CFB ≤0.5) at week 52 was higher with CZP+MTX than with PBO +MTX (82.9% vs 70.7%; p=0.011 by Fisher’s exact test).

### Table 1 Demographics and baseline characteristics (FAS population)

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<th>Parameter</th>
<th>CZP+MTX n=159</th>
<th>PBO+MTX n=157</th>
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<tr>
<td>Age (years)</td>
<td>49.4±10.6</td>
<td>49.0±10.3</td>
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<tr>
<td>Female, n (%)</td>
<td>129 (81.1)</td>
<td>127 (80.9)</td>
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<td>Weight (kg)</td>
<td>57.4±11.3</td>
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<td>BMI (kg/m²)</td>
<td>22.4±3.9</td>
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<td>RA duration (months)*</td>
<td>4.0±2.9</td>
<td>4.3±2.8</td>
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<td>≥3 months, n (%)</td>
<td>60 (37.7)</td>
<td>57 (36.3)</td>
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<td>3–6 months, n (%)</td>
<td>60 (37.7)</td>
<td>56 (35.7)</td>
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<td>6–12 months, n (%)</td>
<td>39 (24.5)</td>
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<td>Previous DMARDs use, n (%)</td>
<td>31 (19.5)</td>
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<td>Steroid use at baseline, n (%)</td>
<td>26 (16.4)</td>
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<td>Anti-CCP antibody positive, n (%)</td>
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<td>157 (100.0)</td>
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<td>High titre (≥3 times of ULN), n (%)</td>
<td>159 (100.0)</td>
<td>157 (100.0)</td>
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<td>CRP (mg/dL)</td>
<td>1.76±1.075</td>
<td>1.82±1.077</td>
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<td>RF positive, n (%)</td>
<td>153 (96.2)</td>
<td>146 (93.0)</td>
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<td>High titre (≥3 times of ULN), n (%)</td>
<td>119 (74.8)</td>
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<td>Titre (U/mL)†</td>
<td>182.5±177.4</td>
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<td>Bone erosion (judged by physician), n (%)</td>
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<td>TJC (2B joints)</td>
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<td>56.7±20.5</td>
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<td>ESR (mm/h)</td>
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<td>CRP (mg/dL)</td>
<td>1.3±1.8</td>
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<td>MMP-3 (mg/mL)‡</td>
<td>11.6±13.4</td>
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<td>PtGADA (ESR)</td>
<td>5.4±1.1</td>
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<td>SDAI</td>
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<td>HAQ-DI score</td>
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<td>mTSS</td>
<td>5.2±8.8</td>
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<td>56 (35.2)</td>
<td>56 (35.7)</td>
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<td>Erosion score</td>
<td>2.2±4.4</td>
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<td>Negative (≤0.5), n (%)</td>
<td>82 (51.6)</td>
<td>80 (50.1)</td>
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<tr>
<td>Joint space narrowing score</td>
<td>2.9±5.8</td>
<td>3.2±8.6</td>
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<tr>
<td>Negative (≤0.5), n (%)</td>
<td>87 (54.7)</td>
<td>82 (52.2)</td>
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<tr>
<td>Average weekly MTX dose (mg/week)</td>
<td>11.6±3.0</td>
<td>11.6±2.7</td>
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Values are mean±SD unless otherwise indicated.
*Time from onset of persistent arthritic symptoms.
†Data exceeding measurement upper limit (≥300 U/mL) are regarded as 300 U/mL.
‡Normal range: 36.9–121 (male), 17.3–59.7 (female) ng/mL.
§BMI, body mass index; CCP, cyclic citrullinated peptide; CRP, C reactive protein; CZP, certolizumab pegol; DAS28 (ESR), Disease Activity Score 28-joint assessment; DMARDs, drugs modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire Disability Index; MMP-3, matrix metalloproteinase-3; mTSS, modified Total Sharp Score; MTX, methotrexate; PBO, placebo; PhGADA, physician global assessment of disease activity; PtGADA, patient’s global assessment of disease activity; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, Simple Disease Activity Index; SJC, swollen joint count; TJC, tender joint count; ULN, upper limit of normal.
Individual patient data are presented in the cumulative probability plot of mTSS CFB at week 52 (figure 2B). In addition, 3.2% of patients with CZP+MTX exhibited RRP (defined as YP >5), compared with 10.8% with PBO+MTX (p=0.008).

Clinical responses
Higher ACR/EULAR remission rates were observed with CZP+MTX compared with PBO+MTX, and a significant difference between the two arms was observed from week 1 in ACR20 and ACR50, and week 2 in ACR70 (figure 3B–D). ACR responses at week 52 in CZP+MTX vs PBO+MTX groups were 78.6% vs 78.8% (p=0.055 by Fisher’s exact test) in ACR20, 73.0% vs 51.6% (p<0.001) in ACR50 and 57.2% vs 34.4% (p<0.001) in ACR70, respectively. A similar time course for HAQ-DI remission rates is shown in figure 3E.

Subgroup analyses for joint damage
Subgroup analyses of mTSS CFB at week 52, stratified by baseline parameters including anti-CCP antibody, RF, C-reactive protein (CRP), matrix metalloproteinase (MMP)-3, HAQ-DI, DAS28 (ESR), mTSS and average concomitant MTX dose are
A comparison of mTSS CFB between treatment groups consistently showed less progression with CZP+MTX compared with PBO+MTX in all categories of these parameters, except for patients with baseline DAS28 (ESR) <3.2 (a small number of patients, n=8). Meanwhile, intraparameter comparison of mTSS CFB revealed a trend of greater mTSS CFB with higher titres of anti-CCP and RF, higher serum CRP and MMP-3, and higher HAQ-DI, DAS28 (ESR) and mTSS at baseline, which was greater in the PBO+MTX group relative to CZP+MTX. In contrast, with regard to concomitant MTX dose, the expected dose-dependent inhibitory effect was not found in either group.

Figure 3  (A) Clinical remission rates at weeks 24 and 52 by Simple Disease Activity Index (SDAI), Boolean and Disease Activity Score 28-joint assessment (DAS28) (erythrocyte sedimentation rate (ESR)) criteria analysed using full analysis set (FAS), last observation carried forward (LOCF) data set. Error bars indicate 95% confidence interval of each remission rate. P values are calculated by Fisher’s exact test. (B-E) Time course of American College of Rheumatology (ACR) response rates of (B) ACR20, (C) ACR50, (D) ACR70 and (E) Health Assessment Questionnaire Disability Index (HAQ-DI) remission rates. *p<0.05 between the groups at each particular time point, calculated by Fisher’s exact test. CZP, certolizumab pegol; MTX, methotrexate; PBO, placebo.
Safety

Study drug exposure during treatment period was greater in the CZP+MTX group (136.2 patient-years) compared with the PBO+MTX group (116.0 patient-years), as more PBO+MTX-treated patients withdrew (mainly due to lack of efficacy). Overall, 153 patients (96.2%) in the CZP+MTX group and 148 patients (94.3%) in the PBO+MTX group reported any AEs. Serious AEs were reported by 13 patients (8.2%) in the CZP+MTX group (136.2 patient-years) compared with the PBO+MTX (55.4%)

Overall incidence of infections and infestations was higher with CZP+MTX (61.0%) compared with PBO+MTX (55.4%), with no difference in the rate of serious infections (3.1% in CZP+MTX vs 4.5% in PBO+MTX). Similar incidences were observed for pneumonia (10 events reported in seven patients [4.4%] for CZP+MTX vs 10 events in eight patients [5.1%] for PBO+MTX), including three cases of Pneumocystis jiroveci pneumonia in each group.

There was no difference in the severity pattern of pneumonia events between CZP+MTX (four serious events) and PBO+MTX (six serious events). There was an apparent correlation between MTX dose and the occurrence of pneumonia since only one patient in each group experienced an event of bacterial pneumonia while receiving low MTX dose (0–8 mg/week) versus five and four patients in the CZP+MTX and PBO+MTX groups, respectively, who experienced ≥1 pneumonia event with high MTX dose (>12–16 mg/week).

The incidence of hepatic events was high (mostly abnormal hepatic function) although it was similar between groups (hepatic disorders: 42.8% with CZP+MTX, 44.6% with PBO+MTX; ‘investigations’ system organ class in hepatic disorders: 42.8% with CZP+MTX, 44.6% with PBO+MTX), indicating that there was no increased risk with the addition of CZP. No patients were withdrawn from the study due to hepatic events, and almost all events were resolved by temporarily discontinuing or reducing MTX dose. No cases of tuberculosis, demyelinating disorders, lupus-like syndrome, serious allergic reactions or serious haematological disorders were reported.

**DISCUSSION**

Compared with similar studies of anti-TNF agents in MTX-naive early RA patients, C-OPERA is characterised by two unique features. First, as far as we know, this is the first randomised controlled trial (RCT) to employ the 2010 ACR/EULAR classification criteria as the main inclusion criteria. Thus, patients enrolled in C-OPERA had very early stages of disease, strictly defined as the time from initiation of persistent arthritic
similar RCTs of biologics,18 DAS28 (ESR): 36.9% at week 52; joint damage inhibition, suggesting that higher doses of MTX may not always be necessary when administered with concomitant anti-TNF agents. However, this is far from conclusive, requires further investigation and may be limited to effects on joint damage progression.

The number of AEs per 100 patient-years was approximately 1.3–1.5 times higher in C-OPERA than the Japan RA Prevention of Structural Damage (J-RAPID) study.12 J-RAPID was similar to C-OPERA; it was conducted in Japanese patients with RA (although these patients had established RA and previous inadequate response to MTX), but average weekly MTX dose was lower (J-RAPID: 6–8 mg/week; C-OPERA: 12 mg/week). In the system, organ classes ‘infections and infestations’, ‘gastrointestinal disorders’ and ‘hepatobiliary disorders’ AEs were more frequently observed in C-OPERA than J-RAPID; these AEs were increased in both PBO and CZP arms, and there was no meaningful difference between the groups. This suggests that the increased frequency of these AEs in C-OPERA may have been associated with the higher MTX dose. Moreover, as all patients were MTX-naïve at study entry, their tolerance to MTX treatment could not be anticipated. Of note, hepatic events, including abnormal investigations, were resolved by temporarily discontinuing or reducing MTX dose and no additional safety risk was identified with CZP based on the lack of a clinically significant difference between the two treatment groups in terms of the incidence or pattern of AEs.

Study limitations included not assessing the effect of CZP monotherapy, which is of interest in early RA treatment. As the current RA treatment recommendations suggest that MTX and/or conventional synthetic DMARDs should be used for initial treatment,3 32 a CZP monotherapy arm was not included in this study. These efficacy and safety findings from C-OPERA in MTX-naïve early RA suggest that CZP could be used as possible first-line treatment concomitantly with MTX in patients with poor prognostic factors, as typified by high-titre anti-CCP antibody. Patients with higher disease activity, functional disability or bone erosion in the early stages of RA will have a higher chance of preventing joint damage and disease progression.

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Patient consent Obtained.

Ethics approval This study was conducted after approval by the Institutional Review Board designated by each study site, in compliance with the ethical principles described in the Declaration of Helsinki and Good Clinical Practice.

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