Maraviroc/raltegravir simplification strategy following 6 months of quadruple therapy with tenofovir/emtricitabine/maraviroc/raltegravir in treatment-naive HIV patients

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Objective: We assessed the virological efficacy of a 6 month maraviroc/raltegravir simplification strategy following 6 months of quadruple therapy combining tenofovir disoproxil fumarate/emtricitabine with maraviroc/raltegravir.

Methods: HIV-1-infected naive patients were enrolled in an open label, single-arm, Phase 2 trial. All patients received maraviroc 300 mg twice daily, raltegravir 400 mg twice daily and tenofovir/emtricitabine for 24 weeks. Patients with stable HIV-RNA <50 copies/mL stopped tenofovir/emtricitabine at week (W) 24 and pursued maraviroc/raltegravir until W48. The primary endpoint was the virological response defined by HIV-RNA <50 copies/mL at W48.

Results: Thirty-three patients were analysed. Patients were mostly male (94%), Caucasians (91%), MSM (82%); their median age was 42 years. At baseline, median CD4 cell count was 453 cells/mm³ and HIV-RNA was 4.3 log copies/mL. All patients had CCR5-tropic viruses by genotyping and phenotyping assays. All but one patient had an HIV-RNA <50 copies/mL at W24 and entered the simplification phase. Virological success was maintained at W48 in 88% (90% CI 79%–97%) of patients. N155H mutation was detected at failure in one patient. No tropism switch was observed. Raltegravir and maraviroc plasma exposure were satisfactory in 92% and 79% of 41 samples from 21 patients. Five severe adverse events (SAEs) were observed up to W48; none was related to the study drugs. Four patients presented grade 3 AEs; none was related to the study. No grade 4 AE was observed. No patient died.

Conclusions: Maraviroc/raltegravir maintenance therapy following a 6 month induction phase with maraviroc/raltegravir/tenofovir/emtricitabine was well tolerated and maintained virological efficacy in these carefully selected patients.

Introduction

Current guidelines recommend the combination of two NRTIs with a boosted PI, a NNRTI or an integrase strand transfer inhibitor (INSTI) as initial ART.1 However, long-term treatment with NRTIs or PIs is often associated with severe toxicity, including renal2 and cardiovascular disorders.3 Maraviroc, a CCR5 receptor antagonist, and raltegravir, an INSTI are both well-tolerated antiretrovirals and have shown high virological efficacy.4,5 The combination has a favourable pharmacokinetic profile.6 In addition to reduced risks of long-term side effects, this combination could offer new perspectives in terms of immunological recovery and prevention
of comorbid conditions. A recent study demonstrated that maraviroc and raltegravir combined with tenofovir disoproxil fumarate/emtricitabine could improve duodenal immunity and decrease plasma inflammatory markers in treatment-naive patients. Moreover, maraviroc might offer neuroprotective benefits in settings in which CCR5 promotes deleterious neuroinflammation and has been associated with significant neurocognitive improvement when added to stable treatment.

However, no clinical data are yet available with this dual combination in naive patients. We report the final results of the No Nuc No Boost study. The objective was to analyse in CCR5-using, HIV-1-infected, treatment-naive patients, the virological efficacy of a 6 month maraviroc/raltegravir simplification strategy following 6 months of quadruple therapy combining tenofovir/emtricitabine with maraviroc/raltegravir.

Patients and methods

Since there were no data on the maraviroc/raltegravir combination in naive patients, we conducted a pilot, Phase 2, multicentre, non-comparative study on a limited number of patients.

Patients

HIV-1-infected, treatment-naive patients were enrolled in an open-label, single-arm, Phase 2 clinical trial from seven HIV centres in France. Inclusion criteria were age ≥18 years, CD4 lymphocyte count >200 cells/mm³, between 10¹ and 10³ HIV-RNA copies/ml, CCR5 tropism determined by Geno2Pheno algorithm and the absence of major NRTI, NNRTI, PI or INI resistance mutations according to the French HIV resistance interpretation’s algorithms v19.11 A conservative false positive rate (FPR) of 20% was chosen for the Geno2Pheno algorithm to maximize the chances of detecting X4-tropic virus sequences.12 R5 genotropisms were confirmed by a phenotropism assay. Pregnant women and patients with decompensated cirrhosis (Child-Pugh stage B or C), or HBV coinfection were excluded as well as patients with haemoglobin <7 g/dL, neutrophil count <500 cells/mm³, platelet count <50,000/mm³, creatinine clearance <50 mL/min, and AST, ALT or bilirubin level above three times the upper limit of normal (ULN).

To prevent exposing patients to an unbalanced regimen, two inclusion phases were planned: a first phase of 10 patients followed by a 6 month break and a second phase with 30 other patients. In case of confirmed virological failure at week (W) 28 in at least 4 of the first 10 patients, the study would have been stopped.

Treatment

All patients received maraviroc 300 mg twice daily, raltegravir 400 mg twice daily and tenofovir 300 mg/emtricitabine 200 mg for 24 weeks. Patients with HIV-RNA <50 copies/mL at W20 and W22 stopped tenofovir/emtricitabine at W24 and pursued maraviroc/raltegravir until W48. If the HIV-RNA level was detectable at W20 and/or week W22, the patient was considered as a virological failure and did not enter into the simplification phase.

Outcomes

The primary endpoint was the proportion of patients without confirmed virological failure at W48 defined as two consecutive HIV-RNA levels >50 copies/mL. Secondary outcomes included the immunological efficacy at W48, time to virological failure, and biological and clinical safety. Due to the lack of data regarding this combination, a close virological monitoring was done, with visits every month throughout the study and additional visits at W22 and W26, before and after the W24 simplification.

Raltegravir and maraviroc trough and peak concentrations were determined using a validated chromatography assay with an external quality assessment (Asqulab, Paris, France) in a sub-group of patients at W12 and W28. A threshold of 50 ng/mL was used for raltegravir and maraviroc trough concentrations. Due to the large variability of pharmacokinetic profiles and in order to investigate possible residual underexposure, peak concentrations were also determined, using thresholds of 240 and 100 ng/mL for raltegravir and maraviroc, respectively.14,15 Overall, drug exposure was considered satisfactory when the trough concentration was above the 50 ng/mL threshold or when peak level was above the respective threshold of both drugs in case of trough concentration between 25 and 50 ng/mL. Compliance was assessed at each visit between W4 and W48 by a self-administered questionnaire. In case of virological failure, genotyping of reverse transcriptase (RT), protease, integrase and gp120 was performed to identify the occurrence of new resistance-associated mutations (RAMs).

Renal function was assessed every 4 weeks by measuring the estimated glomerular filtration rate (eGFR) using the Modification of the Diet in Renal Disease (MDRD) study equation.16 Fasting blood samples were obtained every 3 months for determination of total, HDL and LDL cholesterol, triglycerides, glycaemia and insulinemia. Insulin resistance was assessed using the Homeostasis Model Assessment of insulin resistance (HOMA-IR).17 Body weight, waist circumference, hip circumference and waist-to-hip ratio were determined every 3 months and BMI every 4 weeks.

Statistical analysis

Under the hypothesis of a 80% virological response rate in treatment-naive HIV patients, inclusion of 40 patients in this pilot study will provide a precision of 10.4% (alpha risk 0.10%) meaning that the proportion of success in the sample will vary between 69.4% and 90.4% (90% CI). The pilot design was chosen in order to limit the number of patients exposed to a treatment strategy with which there was no prior experience. Qualitative variables are presented as number of cases and percentages whereas quantitative variables are presented as medians and IQR. An overall analysis was performed based on all patients who received at least one dose of treatment. A planned PP analysis was also conducted based on all patients who entered the simplification strategy at W24. For quantitative biological or clinical parameters, trends over time were tested with a linear regression analysis model using time as an independent variable. A P value <0.05 was considered as statistically significant. All analyses were performed using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA).

Data and safety monitoring board (DSMB)

A DSMB regularly reviewed study data and provided recommendations concerning the continuation, modification or termination of the trial.

Ethics

The study was conducted in accordance with the French legislation concerning clinical trials. It was approved by the local ethics committee (Lyon Sud-East III, ref. 2009-047B) on 1 December 2009 and by the French National Agency for Medicines and Health Products (ANSM, ref. A94271-54) on 28 December 2009. It was registered at the European Clinical Trials Database (EudraCT): 2009-016480-11, and at clinicaltrials.gov: NCT01291459. All patients provided their written informed consent.

Results

Patients’ characteristics

Between October 2011 and December 2013, 55 patients were screened, 34 were recruited and 1 withdrew consent after initiation of treatment, leading to 33 analysed patients, recruited.
Maraviroc/raltegravir simplification strategy

from seven centres (Figure 1). Reasons for non-inclusion were mostly non-R5 viruses (n=13) and/or HIV-RNA outside limits (n=4), and consent withdrawal before day 0 (n=3). Patients were mostly males (94%), Caucasians (91%), MSM (82%), of median age 42 years (Table 1). At baseline, median CD4 cell count was 453 cells/mm³ and median HIV-RNA level was 4.3 log copies/mL. A non-B subtype was observed in 36% of patients. All R5 genotropisms were confirmed by a phenotropism assay. However, 12 of the 13 patients excluded by the genotypropism assay were determined to be infected with R5 viruses by the phenotypropism assay.

Virological efficacy

Thirty-two of 33 patients (97%) had an HIV-RNA <50 copies/mL at W20 and W22 and entered the simplification phase of the study. One patient still had a detectable HIV RNA level at W24 (first detectable at W20) and did not enter the simplification phase. Among 32 patients who simplified their treatment, 29 maintained HIV-RNA <50 copies/mL until W48. The overall virological response rate at W48 was 88% (90% CI 79%–97%) (29/33 patients) and 91% (90% CI 82%–99%) (29/32 patients) in the PP analysis (Figure 2).

Description of virological failures

Four patients had a virological failure, one before the simplification phase at W20 and three during the simplification phase at W36, W44 and W48 (Table 2). The W48 failure could not be confirmed since the patient’s treatment was modified the same day and a single blip could not be excluded. Failure at W36 was presumed secondary to non-compliance following relapse of chronic alcoholism. Only one patient exhibited an integrase resistance mutation at failure at W44 (N155H).

Immunological efficacy

The median CD4 cell count increased smoothly from 443 cells/mm³ at baseline to 715 cells/mm³ at W48 (P<0.001). During the same period, the proportion of patients with CD4 cell count ≥500 cells/mm³ increased from 36% to 88% (P<0.001). Similarly, the CD4/CD8 ratio also increased regularly from 0.53 to 0.78 at W48 (P<0.001).

Pharmacokinetic analysis

Forty-one plasma samples from 21 patients enrolled in the second phase of the study were analysed for maraviroc and raltegravir concentrations (Table S1, available as Supplementary data at JAC Online). Raltegravir trough concentrations were >50 ng/mL in 89% of samples (33/37), while maraviroc trough concentrations were above this threshold in only 59% of samples (22/37). Raltegravir peak concentrations were >240 ng/mL in 77% of samples (27/35) and maraviroc peak concentrations were >100 ng/mL in 97% of samples (33/34). Overall, exposure was considered satisfactory in 92% of samples for raltegravir and in 79% of samples for maraviroc.

Safety

One hundred and fifty-seven adverse events (AEs) were reported in 33 patients. Of these AEs, 87 were of grade 1, 66 of grade 2 and 4 of grade 3 (Table 3). Four patients presented grade 3 AEs, none related to the study. No grade 4 AE was observed. Five severe adverse events (SAEs) were observed until W48, all resulting in hospitalization. One patient had a depressive episode, one a drug dependence, one had severe anxiety, one had hyperalgesia

Table 1. Patients’ characteristics at baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>31 (94)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>30 (91)</td>
</tr>
<tr>
<td>Age (years), median (IQR)</td>
<td>42 (34–48)</td>
</tr>
<tr>
<td>Risk factor for HIV infection (MSM), n (%)</td>
<td>27 (82)</td>
</tr>
<tr>
<td>Duration of HIV infection (months), median (IQR)</td>
<td>8.7 (3.4 – 36.3)</td>
</tr>
<tr>
<td>CD4 count (cells/mm³), median (IQR)</td>
<td>453 (369 – 550)</td>
</tr>
<tr>
<td>CD4 (%), median (IQR)</td>
<td>28 (23 – 33)</td>
</tr>
<tr>
<td>HIV-RNA (log copies/mL), median (IQR)</td>
<td>4.3 (3.8 – 4.5)</td>
</tr>
<tr>
<td>Geno2Pheno FPR, median (IQR)</td>
<td>4.72 (31.8 – 78.1)</td>
</tr>
<tr>
<td>Phenotropism R5, n (%)</td>
<td>33 (100)</td>
</tr>
<tr>
<td>Genotype B, n (%)</td>
<td>20 (61)</td>
</tr>
</tbody>
</table>

Figure 1. Study flow chart.

Figure 2. Proportion of patients with virological success (confirmed HIV-RNA <50 copies/mL) over time.
and one had a uterine polyp requiring endometrial ablation. None of these SAEs was related to the study drugs. No patient died. Table S2 shows that most frequent AEs by system organ class (SOC) of the MedDRA classification\(^{18}\) were infections, gastrointestinal disorders, metabolism and nutrition disorders, and psychiatric disorders.

The eGFR declined slightly from baseline [median (IQR) 114 mL/min/1.73 m\(^2\) (100–125)] to W24 [102 mL/min/1.73 m\(^2\) (87–117)] and increased back at W48 [106 mL/min/1.73 m\(^2\) (92–117)], resulting in an overall non-significant effect (\(P = 0.60\)). No effect was observed regarding total cholesterol [baseline 4.6 mmol/L (4.0–5.4), W48 4.8 mmol/L (4.3–5.5), \(P = 0.13\)], LDL cholesterol [baseline 2.8 mmol/L (2.4–3.1), W48 2.8 mmol/L (2.3–3.2), \(P = 0.450\)], triglycerides [baseline 1.1 mmol/L (0.7–1.8), W48 1.1 mmol/L (0.8–1.6), \(P = 0.559\)], glycaemia [baseline 4.7 mmol/L (4.3–5.2), W48 5.1 mmol/L (4.5–5.4), \(P = 0.32\)], insulinaemia [baseline 5.1 mmol/L (4.0–7.0), W48 6.0 mmol/L (3.9–7.8), \(P = 0.65\)] or the HOMA-IR [baseline 1.1 (0.8–1.5), W48 1.2 (0.8–1.9), \(P = 0.65\)]. A slight increase in HDL cholesterol was observed during the study [baseline 1.1 mmol/L (1.0–1.4), W48 1.4 mmol/L (1.1–1.7), \(P = 0.006\)]. No effect was observed regarding BMI [baseline 23 kg/m\(^2\) (20–24), W48 23 kg/m\(^2\) (21–25), \(P = 0.792\)], waist circumference [baseline 85 cm (78–91), W48 90 cm (81–95), \(P = 0.06\)], hip circumference [baseline 92 cm (90–98), W48 95 cm (90–100), \(P = 0.14\)] or the waist-to-hip ratio [baseline 0.90 (0.85–0.95), W48 0.93 (0.88–0.99), \(P = 0.41\)].

**Compliance**

At each visit, 79%–93% of patients reported a strict adherence to the therapeutic schedule during the past 4 weeks (Figure 3). However, only 21% of patients reported a strict respect of the schedule at each of the 12 visits and 67% at 10 or more visits. No difference in compliance was observed between the first 24 weeks (quadruple therapy) and the simplification phase and between the different drugs.

**Discussion**

Our results indicate that the dual combination maraviroc/raltegravir simplification strategy following a 6 month induction phase with maraviroc/raltegravir/tenofovir/emtricitabine was able to maintain virological efficacy (<50 copies/mL) at W48 in 88% of patients (overall analysis) and in 91% of patients entering the simplification phase (PP analysis). Moreover, the maraviroc/raltegravir combination was well tolerated without particular toxicity.

The recently published ROCnRAL study tested a 24 week maraviroc/raltegravir combination in HIV-infected patients previously treated with lipohypertrophy.\(^{12}\) Despite an overall improvement in lipid profile and bone mineral density, the authors reported, at W24, five patients (11%) experiencing virological failure and two patients (4.5%) with treatment cessation following development of adverse events. Among patients with virological failure, three had a raltegravir resistance mutation whereas two had a CXCR4 tropism. Following recommendation from the ROCnRAL DSMB, the study was stopped prematurely. Despite these results being published while our study was ongoing, the good virological and tolerability results in our study led our DSMB to approve the

<table>
<thead>
<tr>
<th>Table 2. Description of cases with virological failure</th>
</tr>
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<tbody>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>------------------------------------------------------</td>
</tr>
<tr>
<td>BKVY</td>
</tr>
<tr>
<td>TBVH</td>
</tr>
<tr>
<td>SCAX</td>
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<tr>
<td>ZMNN</td>
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</tbody>
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FPR, false positive rate; MVC, maraviroc; ND, not done; RAL, raltegravir; RAMs, resistance-associated mutations.
Table 3. Safety: number of adverse events (AEs) occurring between day 0 and week 48 (n=157)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE grade 1</td>
<td>87</td>
</tr>
<tr>
<td>AE grade 2</td>
<td>66</td>
</tr>
<tr>
<td>AE grade 3 clinical</td>
<td>2</td>
</tr>
<tr>
<td>biological</td>
<td>2</td>
</tr>
<tr>
<td>(anxiety, alcoholism)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>5</td>
</tr>
<tr>
<td>Serious adverse event (related)</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
<tr>
<td>Treatment discontinuation (related)</td>
<td>0</td>
</tr>
<tr>
<td>Biological AE grade 4</td>
<td>0</td>
</tr>
<tr>
<td>Unexpected AE</td>
<td>0</td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min</td>
<td>0</td>
</tr>
<tr>
<td>Glycosuria &gt;1+</td>
<td>0</td>
</tr>
<tr>
<td>Proteinuria &gt;1+</td>
<td>3</td>
</tr>
<tr>
<td>(+++ : 2; ++++ : 1)</td>
<td></td>
</tr>
</tbody>
</table>

CK, creatine kinase; eGFR, estimated glomerular filtration rate.

Figure 3. Compliance with therapeutic schedule during the previous month at each visit. Strict compliance represents strict respect for the therapeutic schedule. Global compliance means strict respect for the therapeutic schedule with a few exceptions.

continuation of the study. Several parameters could explain the differences observed between the ROCnRAL and the present study. (i) The populations differed in their baseline characteristics—patients from the ROCnRAL study were indeed pretreated, had lower nadir CD4 (median 210 cells/mm\(^3\) versus 453 cells/mm\(^3\) in the present study), and longer HIV infection (20 years versus 8.7 months). Previous studies have indeed shown that low nadir CD4 was associated with an increased proportion of CXCR4 tropism. Since maraviroc is a CCR5 receptor antagonist, this phenomenon would increase the risk of having a raltegravir monotherapy on such viruses, resulting in an increased risk of virological failure. However, in the ROCnRAL study, presence of minority X4-tropic viral variants was not associated with virological failure. (ii) Since the patients were already under antiretroviral treatment in the ROCnRAL study, the tropism was determined on cellular proviral DNA, whilst it was determined on plasma RNA in our study. It has been suggested that proviral DNA was not as representative of the different viral populations as RNA, which could explain the emergence of non-R5 viruses at failure in the ROCnRAL study. (iii) Another possible explanation could be a lower treatment compliance in the ROCnRAL study in which patients switched from a once-a-day regimen to a twice-daily maraviroc/raltegravir intake.

Unlike in the ROCnRAL study, virological failure resulted in the selection of resistance mutations in the integrase gene in only one patient. The close monitoring of the patients who were followed-up every month throughout the study could explain: (i) better compliance; (ii) the ability to detect low-level replication and potential blips; and (iii) could have also limited the emergence of mutations by limiting the time during which the virus was able to replicate under treatment.

Our results show a smooth increase in the CD4 cell count and in the CD4/CD8 ratio, even after entering into the simplification phase. Once again, these results contradict those of the ROCnRAL study in which the switch to maraviroc/raltegravir dual therapy resulted in a decrease in the CD4/CD8 ratio, which is possibly explained by a slight loss of virus control. In the present study, the proposed therapeutic strategy resulted in immune restoration with a 50% increase of the CD4 cell count between baseline and W48, as expected during antiretroviral therapy.

Similar to the ROCnRAL study, no significant drug-drug interaction between maraviroc and raltegravir was observed in our study. Despite the fact that maraviroc trough concentrations <50 ng/mL threshold were observed in 41% of patients, the majority of patients maintained virological efficacy through W48 and maraviroc exposure did not seem associated with virological failure. Since the 50 ng/mL threshold was defined for treatment-experienced patients, these results, as well as the absence of relationship between maraviroc exposure and maraviroc receptor occupancy, suggest that a lower threshold could probably be used in naive patients.

No new or unexpected toxicity was observed during the study, indicating that the tolerability of the combination was similar to the tolerability of each individual drug. The renal and the metabolic tolerability of the strategy appeared particularly interesting, since the slight decrease in eGFR observed after the 6 month induction phase to replication with a 50% increase of the CD4 cell count between baseline and W48, as expected during antiretroviral therapy.

No new or unexpected toxicity was observed during the study, indicating that the tolerability of the combination was similar to the tolerability of each individual drug. The renal and the metabolic tolerability of the strategy appeared particularly interesting, since the slight decrease in eGFR observed after the 6 month induction phase to replication with a 50% increase of the CD4 cell count between baseline and W48, as expected during antiretroviral therapy.

Our study has some limitations. (i) The study was not comparative. This pilot design was chosen in order to limit the number of patients exposed to a treatment of which we had no prior experience. Moreover, a comparison of groups of limited sample
size was not relevant. However, the virological efficacy appears high in this study, in line with other current antiretroviral treatments. (ii) Only 34 patients were enrolled instead of the 40 planned initially. After the interruption of the ROCnRAL study, patients’ enrolment became difficult in some centres. In order not to extend the study duration too much, we decided to stop the inclusion after 34 patients. This had no major impact on the precision of the results since the decreased precision resulting from the lower sample size was counterbalanced by a higher precision resulting from a higher-than-expected virological response rate (88% instead of 80%). (iii) We used a conservative approach for the selection of patients by excluding patients with high viral load and/or low CD4. Therefore, the conclusions of the study cannot, at this stage, be generalized to the entire HIV population. (iv) The FPR of 20% was retained for the genotypism assay instead of the usual 10% rate, in order to strictly enrol R5-infected patients. This choice could have resulted in excluding from the study patients infected by R5 viruses, while determined as non-R5 by this more stringent condition. Indeed, most of the patients excluded from the study on the basis of the genotypism assay were determined as being infected by R5 viruses using a phenotypism assay. We therefore cannot conclude if these results could be translated using a different assay for selecting the patients. (v) Both maraviroc and raltegravir were given twice a day in the study, as recommended. Since most current antiretroviral treatments are now administered once a day, which may result in a slightly better compliance,26 this scheme could explain the relatively disappointing results of compliance obtained by the self-administered questionnaire. (vi) The study did not include a bone mineral density analysis and we cannot reach any conclusions on the effect of the combination on this parameter.

In conclusion, the maraviroc/raltegravir maintenance therapy following a 6 month induction phase with tenofovir/emtricitabine/maraviroc/raltegravir was well tolerated and maintained virological efficacy in the majority of cases in these carefully selected patients infected with CCR5 viruses. Only one patient exhibited an integrase resistance mutation at failure at W44 (N155H). This therapeutic schedule should not be recommended in all patients but could be an option in selected patients with optimal expected compliance.

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Members of the No Nu No Boost Study Group

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Supplementary data
Tables S1 and S2 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References