Phase 1 Clinical Trial of a Conditionally Replication-Defective Human Cytomegalovirus (CMV) Vaccine in CMV-Seronegative Subjects

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Background. A conditionally replication-defective human cytomegalovirus (CMV) vaccine (V160) derived from AD169 and genetically engineered to express CMV pentameric complex (gH/gL/pUL128/pUL130/pUL131) was developed and evaluated for phase 1 vaccine safety and immunogenicity in CMV-seronegative and CMV-seropositive adults.

Methods. Subjects received 3 doses of V160 or placebo on day 1, month 1, and month 6. Four vaccine dose levels, formulated with or without aluminum phosphate adjuvant, were evaluated. Injection-site and systemic adverse events (AEs) and vaccine viral shedding were monitored. CMV-specific cellular and humoral responses were measured by interferon-gamma ELISPOT and virus neutralization assay up to 12 months after last dose.

Results. V160 was generally well-tolerated, with no serious AEs observed. Transient, mild-to-moderate injection-site and systemic AEs were reported more frequently in vaccinated subjects than placebo. Vaccine viral shedding was not detected in any subject, confirming the nonreplicating feature of V160. Robust neutralizing antibody titers were elicited and maintained through 12 months postvaccination. Cellular responses to structural and nonstructural viral proteins were observed, indicating de novo expression of viral genes postvaccination.

Conclusions. V160 displayed an acceptable safety profile. Levels of neutralizing antibodies and T-cell responses in CMV-seronegative subjects were within ranges observed following natural CMV infection.

Clinical Trial Registration. NCT01986010.

Keywords. cytomegalovirus; vaccine; immunogenicity; safety.

Cytomegalovirus (CMV) is a prototypical beta-herpes virus ubiquitous among humans and is spread through close interpersonal contact via infectious body fluids [1]. A hallmark of CMV infection is that it can remain in the body in a latent (inactive) state; periodic reactivation is thought to induce robust and broad immune responses [2]. In healthy individuals, CMV infection is usually asymptomatic; however, infection can cause serious health problems for individuals with weakened immune systems (ie, transplant and human immunodeficiency virus-infected patients) and for infants infected in utero [3]. CMV infection in women during pregnancy is the leading cause of viral congenital infection, which can lead to a range of abnormalities in newborns (including hearing loss, visual impairment, and cognitive impairment) as well as occasional fetal or infant death [4]. Congenital CMV occurs in 0.6% to 0.7% of newborns in developed countries [1, 5], which translates to approximately 20 000 to 40 000 congenital infections per year in the United States [4, 6–8]. In Europe, the number of patients at risk of congenital CMV infection following primary CMV infection was estimated at less than 1 in 10 000 people, corresponding to approximately 50 000 congenital CMV infections annually [9].

Although the protective efficacy of natural immunity against reinfection and congenital transmission is not fully understood [10], preexisting immunity to CMV is considered to be effective against new CMV acquisition. Congenital infection is approximately 69% lower among children born to women who are seropositive prior to pregnancy as compared with those born to seronegative mothers who acquire CMV during pregnancy [11, 12]. Additionally, CMV-seropositive recipients of solid organ transplants are partially protected from CMV infection posttransplantation [13]. Finally, naturally seropositive mothers are over 80% protected against acquiring CMV from their infected children [14]. Because natural CMV infection can elicit robust immune responses, including both T-cell
and humoral responses [6–8], it is hypothesized that a whole-virus vaccine, if appropriately designed, may induce immune responses resembling those of natural infection [15]. With this immunological goal in mind, a genetically engineered CMV designated V160 was constructed from live attenuated AD169 strain with specific modifications to improve its immunogenicity and safety. Immunogenicity was enhanced through restoration of viral pentameric complex (gH/gL/pUL128/pUL130/pUL131), which has been recognized as a dominant target for neutralizing antibodies (NAbs) in natural immunity [16]. To improve safety, the virus strain was further engineered with a chemically controlled protein stabilization switch [17], which renders 2 viral proteins essential to viral replication prone to degradation unless a synthetic compound named Shield-1 is provided; as a result, V160 can only replicate when Shield-1 is present in viral culture [17–19]. V160 contains and can therefore express major antigens known to be targets for antibody and T-cell responses in natural infection.

Because CMV infections are species restricted, this phase 1 trial represented the first opportunity to evaluate the elements of the V160 design in vivo. The objective of the current study was to assess immunogenicity, safety, and tolerability profiles of various doses, formulations, and routes of administration of V160 administered as a 3-dose regimen in CMV-seropositive and CMV-seronegative healthy adult volunteers. This manuscript provides safety and immunogenicity results following vaccination with V160 of CMV-seronegative healthy adult subjects.

**METHODS**

**Study Design**

This trial was a 2-part, double-blind, randomized, placebo-controlled, dose escalation multicenter study conducted at 9 clinical sites in the United States between November 2013 and March 2017 (NCT01986010). The study was performed in conformance with standards of Good Clinical Practice, and the protocol was reviewed and approved by an independent institutional review board/ethics review committee. Subjects provided written informed consent before participation. Visit assessments are summarized in Supplementary Figure 1.

Part 1 of the study evaluated immunogenicity and safety of 4 different dose levels (10, 30, 100, and 250 units/dose) of V160 formulated with or without aluminum phosphate adjuvant, when administered intramuscularly (IM) as a 3-dose regimen at day 1, month 1, and month 6 in CMV-seropositive subjects and CMV-seronegative subjects (Supplementary Figure 2A). Vaccine units of antigen were measured by a sandwich enzyme-linked immunosorbent assay (ELISA). This ELISA captures vaccine particles using a monoclonal antibody specific to the pentameric complex (gH/gL/pUL128/pUL130/pUL131) and detects the captured particles using Cytogam®. A capture monoclonal antibody specific to the pentameric complex was used to ensure that the pentameric complex is present on vaccine particles. The ELISA reference standard was assigned an antigen concentration (U/mL) based on the total protein concentration (μg/mL) of the same material. Aluminum phosphate adjuvant was investigated in this study because preclinical work had demonstrated a benefit of adjuvant in the immune response. Subjects were randomized according to their CMV serostatus and gender (Supplementary Table 1). Each antigen dose level of V160 and dose escalation was first evaluated in CMV-seropositive volunteers, then CMV-seronegative volunteers. Each dose level was designed to enroll 10 subjects who received V160 and 4 subjects who received placebo (saline solution).

Part 2 of the study evaluated a 3-dose regimen of a medium dose (30 units) of V160 or placebo administered intradermally (ID) using the same dosing schedule in CMV-seropositive (stage 5A) and CMV-seronegative (stage 5B) subjects (Supplementary Figure 2B; Supplementary Table 1). Parts 1 and 2 were conducted in parallel; however, initiation of stage 5A was dependent upon safety data evaluation from subjects in stage 1A by the standing internal data monitoring committee.

**Subjects**

Healthy males or females eligible for inclusion in the study were ≥18 years of age with body weight ≥50 kg and body mass index (BMI) 19–32 kg/m² and were serologically confirmed as either CMV seropositive or CMV seronegative. Participants of reproductive age agreed to use contraception during the vaccination and for 4 weeks after receipt of last dose of study drug. Subjects were excluded from the trial if they had previously received any CMV vaccine, had a history of allergic reaction or anaphylactic/anaphylactoid reaction that required medical attention to any vaccine component, or had a history of any severe allergic reaction. Other exclusion criteria included recent history of febrile illness (<72 hours); receipt of any live virus vaccine (4 weeks before through 1 month after study vaccine), inactivated vaccine (7 days before through 7 days after study vaccine), or immune globulin or blood product (within 90 days); known or suspected impairment of immunologic function; and recent receipt of immunosuppressive therapies.

**Immunogenicity Analyses**

Results focused on the per-protocol immunogenicity population that included all subjects who received all 3 doses of either V160 or placebo and had at least 1 serology result. CMV-specific NAb titers were measured using a microneutralization assay [20]. NAbs are presented as NT<sub>50</sub> titers, defined as the reciprocal serum dilution to reduce 50% viral infection of the CMV AD169rev strain in ARPE-19 cells [20]. For this assay, a vaccine response was defined as NT<sub>50</sub> ≥250 in a CMV-seronegative subject. CMV-specific cellular immune responses were measured using enzyme-linked immunosorbent spot assays (ELISPOT), quantifying the number of interferon-gamma (IFN-γ) secreting...
cells from peripheral blood mononuclear cells (PBMCs) after in vitro stimulation with selected CMV antigens [21]. The antigens tested included purified CMV virus, and pools of 15-mer peptides overlapping by 11 amino acids corresponding to open reading frames of immediate-early protein-1 (IE1), IE2, phosphorylated protein 65 (pp65), or glycoprotein B (gB) antigens. Responses are presented as spot forming units (cells) per 10^6 PBMC (SFU/10^6 PBMCs).

**Safety Analyses**

Safety analysis included subjects who received ≥1 dose of study vaccine or placebo. Adverse events (AEs) including injection-site and noninjection-site AEs were collected for 14 days following each vaccination. All AEs were assessed for toxicity grade, severity, and causality relationship to study vaccine. Saliva and urine samples were collected on days 7 and 14 after the first vaccination to evaluate viral shedding using polymerase chain reaction (PCR) method with primers common to all CMV. A secondary PCR assay designed with additional primer sets differentiated wild-type from vaccine-type CMV.

**Statistical Methods**

The primary immunogenicity analysis time point was immune responses measured at 1 month postdose 3 (PD3). For this, point estimates and 95% confidence intervals (CI) of NAb geometric mean titers (GMTs) and IFN-γ-secreting cell geometric mean counts (GMCs) were calculated. The 95% CI of GMTs and GMCs were computed by taking the antilogarithm of lower and upper limits of the T-distribution–based 95% CI of log-transformed NAbs and IFN-γ–secreting cells. For all other time points, point estimates of NAb GMTs and IFN-γ–secreting cell GMCs were calculated and reported.

**RESULTS**

**Study Subjects**

A total of 95 CMV-seropositive and 95 CMV-seronegative subjects were enrolled in the study, and 161 subjects (84.7%) received all 3 vaccinations. The number of subjects who discontinued from the trial and reasons for discontinuation were comparable across vaccination groups within each cohort (Figure 1). Subject characteristics are summarized in Table 1. The distributions of study subjects by gender, age, race, and ethnicity were comparable between the CMV-seropositive and CMV-seronegative cohorts (Table 1).

**Neutralizing Antibody and Cellular Immune Responses in Seronegative Subjects Following Intramuscular Vaccine Administration**

All formulations of V160 with or without aluminum phosphate adjuvant were immunogenic in CMV-seronegative individuals. Following vaccination, NAb titers increased with each subsequent vaccination, responses peaked at month 7, then declined and plateaued thereafter (Figure 2). Regarding vaccine responder rates (ie, NT_{50} ≥ 250), no more than 10% of initially CMV-seronegative subjects had NAb titer above this prespecified threshold at baseline. Following vaccination, 100% of vaccine recipients were seropositive at month 7 and a majority remained seropositive at month 12 and month 18 (Figure 3). At month 7, highest NAb titers were measured in the 100-unit formulation with aluminum phosphate adjuvant, with GMT closely approaching the corresponding baseline (ie, at day 1 prior to vaccination dose 1) GMT in CMV-seropositive individuals, the benchmark of natural immunity to CMV (Figure 4). The 95% CI estimates of NAb GMTs in other V160 formulations, except the unadjuvanted 10- and 100-unit formulations, overlap the 95% CI estimate of baseline NAb GMT in CMV-seropositive individuals.

All formulations of V160 with or without aluminum phosphate adjuvant induced cell-mediated immune (CMI) response to CMV, IE1, and pp65 antigens, increasing with each subsequent vaccination, and unlike the NAb response, continued to increase beyond 1 month PD3 in several V160 formulation groups (Figure 2). Study results suggested that ELISPOT >4-fold rise relative to mock and >300 SFU/10^6 PBMCs is an acceptable cutpoint that differentiates CMI responses in placebo recipients.

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<tr>
<th>Table 1. Subject Characteristics</th>
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<td>Seropositive (n = 95)</td>
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<td>Female</td>
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<td><strong>Age, years, n (%)</strong></td>
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<tr>
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<tr>
<td>Black/African American</td>
</tr>
<tr>
<td>White</td>
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<td>Other</td>
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compared to V160 recipients. CMI responder rates (SFU/10^6 PBMC ≥ 300) increased with each subsequent vaccination, and continued to increase beyond month 7 in several V160 formulation groups. For CMI responders that were seropositive at month 7, a majority remained seropositive at month 12 and month 18. (Figure 3). At month 7, the IE1 and pp65 GMCs in all V160 formulation groups approached or exceeded the corresponding baseline GMCs in CMV-seropositive individuals; the 95% CI of the GMCs in V160 formulation groups overlap or were above the corresponding baseline 95% CI GMCs in CMV-seropositive individuals. Similar trends were observed for the CMV antigen for most formulation groups (Figure 4).

Neutralizing Antibody and Cellular Immune Responses in Seronegative Subjects Following Intradermal Vaccine Administration

Intradermal administration of 30 units of V160 induced humoral and CMI responses in seronegative subjects. NAb titers and IFN-γ secreting cells increased with each subsequent vaccination, peaked at 1 month PD3, and declined over the following 12 months PD3 (Supplementary Figure 3). At month 7, NAb GMT in seronegative individuals appeared to be higher than the corresponding baseline GMT in CMV-seropositive individuals and the 95% CI estimate of NAb GMT in seronegative individuals overlap the 95% CI estimate of baseline NAb GMT in CMV-seropositive individuals;

CMV-specific GMCs in V160-vaccinated seronegative individuals approached or exceeded the corresponding baseline GMCs in CMV-seropositive individuals, especially for responses to IE1 peptides; the 95% CI of the GMCs in seronegative individuals overlap or were above the corresponding baseline 95% CI GMC in CMV-seropositive individuals (Supplementary Figure 4).

Safety

Injection-site and systemic AEs are summarized in Table 2. Most subjects (58%–100% in the seropositive and 67%–100% in the seronegative cohorts) reported an injection-site AE during the 14 days after V160 vaccination. Pain was the most frequently reported injection-site AE in the IM administration groups, whereas erythema was the most common injection-site event in the ID administration groups. Most injection-site events were mild to moderate in intensity, and 2 subjects in each cohort receiving IM vaccine reported severe injection-site pain.

Most subjects (64%–91% in the seropositive and 67%–100% in the seronegative cohorts) reported at least 1 systemic AE. Rates for subjects receiving placebo ranged from 50% to 58% for the seropositive cohort and from 56% to 100% for the seronegative cohort. The most commonly reported systemic AEs in both cohorts were fatigue and headache. Most events
were mild to moderate in intensity. Four subjects in the seropositive cohort experienced a severe systemic AE (myalgia \[n = 2\]; headache \[n = 1\]; and fatigue and myalgia \[n = 1\]). Seven subjects in the seronegative cohort experienced a severe systemic AE (fatigue and headache \[n = 1\]; myalgia and headache \[n = 1\]; headache \[n = 2\]; fatigue and myalgia \[n = 1\]; and fatigue \[n = 2\]). Four subjects (seronegative cohort \[n = 3\], seropositive cohort \[n = 1\]) discontinued vaccination due to an AE (severe injection-site pain \[n = 1\]; mild injection-site reaction \[n = 1\]; moderate myalgia \[n = 1\]; and moderate malaise \[n = 1\]). Body temperature \(\geq 38.0°C\) was observed in 4% and 9% of seropositive and seronegative subjects, respectively, and no subject in either cohort experienced severe fever (ie, \(\geq40.0°C\)).

During the study, all subjects from both the CMV-seropositive and CMV-seronegative cohorts were closely followed for viral shedding in saliva and urine samples, as viral shedding was considered reliable evidence for active viral replication. CMV shedding was observed in 1 subject in the CMV-seropositive cohort, and was determined to be wild-type virus. No vaccine-type viral shedding was observed in 147 subjects who received V160 during the study, and this result confirmed the nonreplicating feature of V160.

### DISCUSSION

A vaccine to prevent congenital CMV has been identified as an urgent public health need due to the devastating consequences of congenital infection. Previous vaccine efforts in the past 5 decades have produced 2 candidates, live attenuated virus Towne vaccine and recombinant gB/MF59 vaccine, advanced to clinical proof-of-concept studies [22]. However, both demonstrated modest efficacy against CMV acquisition in CMV-seronegative women. Both these vaccines lacked expression of the viral pentameric complex, a tropism determinant for CMV to infect epithelial and endothelial cells [23, 24], and a key antigen for potent neutralizing antibodies observed during natural infection [25–28]. The vaccines both induced relatively low titers of neutralizing antibodies, especially in epithelial cells, as compared to those seen in CMV-seropositive subjects [29]. V160 is the first vaccine candidate designed to express the pentameric complex, and the results in this first-in-human evaluation confirm the importance of the pentameric complex in eliciting potent neutralizing titers against viral infection of human epithelial cells observed in preclinical evaluations [16, 17].

In women, preconception immunity to CMV, as well as the early emergence of anti-CMV responses after primary CMV
infection, has been associated with protection against maternal-fetal CMV transmission [11, 12, 30, 31]. Although congenital infection has been observed in cases of nonprimary CMV infection in women during pregnancy [32], in the absence of an immunologic correlate of protection for prevention of maternal-fetal CMV transmission, natural immunity to CMV remains an important benchmark for evaluation of a vaccine [10, 15]. V160 is a whole-virus vaccine, designed to present most biochemically definable antigens that are commonly presented during natural CMV infection [26]. Because critical components of protective anti-CMV immunity against congenital transmission are still unknown, a whole-virus vaccine such as V160 may have the best probability to elicit adaptive immunity closely resembling those seen in natural immunity. Indeed, our evaluation confirmed that most V160 formulations induced immune responses at 1 month PD3 in the range of those seen in natural immunity, both for neutralizing antibody and T-cell responses. It is not unexpected that V160 immunity does not exceed that induced by natural CMV infection. Durable vaccine-mediated immunity will be key to providing protection against maternal-fetal transmission.

Further work on the persistence of the V160-mediated immunity will be undertaken in future studies.

Safety is always a key concern in developing whole-virus vaccines. Although V160 was developed from AD169, which was shown to be safe in 2 small phase 1 studies, there was theoretical concern that restored pentameric complex may affect its safety profile. Thus, to increase the safety margin, a chemically controlled protein stabilization switch design was employed in V160, which allowed the control viral replication with the synthetic chemical Shield-1 [17]. In general, V160 demonstrated acceptable safety and tolerability profiles in all dose groups, especially when compared to placebo recipients. In addition, although most subjects reported injection-site AEs, as expected of any injectable vaccine, there was no increase in rates of AEs with increased vaccine dose. Importantly, there was no V160 excretion in urine and saliva in CMV-seronegative subjects with V160 vaccination, confirming the replication-defective design of the vaccine.

In this study, we only measured neutralizing titers in human ARPE-19 retinal pigment epithelial cells because the ability to produce antibodies that can neutralize viral entry into epithelial
cells is more relevant to vaccine efficacy [29]. Several studies have demonstrated the importance of the pentameric complex as primary target for human neutralizing antibodies against viral infection of epithelial cells as opposed to gB [27, 28]. V160-induced T-cells could recognize whole-virus antigen as expected; at individual antigen level, responses were mostly focused on IE1 and pp65, rather than IE2 and gB. This focused pattern of antigen recognition to IE1 and pp65 was different from what has been reported for CMV-seropositive subjects [8], as seen at baseline among CMV-seropositive subjects in our study. These observations have certain implications. First, V160, although not replicating, can elicit T-cell responses towards antigens such as nonstructural antigen IE1, which would require de novo expression after vaccination, and confirmed what we have observed in nonhuman primate studies [17]. Second, responses were mostly focused on IE1 and pp65, but not to IE2 and gB. This pattern of T-cell recognition postvaccination suggested that viral antigens ample for T-cell responses were limited to IE1 and pp65, possibly due to the genetic chemical switch mechanism, which was expected to reduce viral gene expression downstream of IE1 [17]. Of course, more detailed analysis of T-cell immune profiles would be needed to delineate the mechanism of this antigen targeting preference. A limitation of this study was that selected CMV antigens were tested for immune response and only increases in immune response from baseline were presented.

In summary, results of this study indicate that V160 is generally well tolerated and induces both CMV-specific NAbs and T-cell responses similar to those induced by natural infection. More specifically, V160 induces neutralizing antibodies targeting epithelial cell infection, which are thought to prevent viral spread in vivo and infection of human placental cytotrophoblasts, a critical step in CMV transmission to the fetus [25, 31]. These encouraging immune responses, along with the acceptable safety profiles, have established the basis for further evaluation of V160 for its efficacy to prevent CMV acquisition in CMV-seronegative women of child-bearing age.

### Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

### Notes

**Author contributions.** S. P. A. and L. M.: Conception, design or planning of the study, acquisition of the data, analysis of the data, interpretation of the results, drafting of the manuscript. N. L.: Conception, design or planning of the study, drafting of the manuscript. A. C.: Conception, design or planning of the study,

### Table 2. Summary of Adverse Events

<table>
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<tr>
<th></th>
<th>V160 10 units</th>
<th>V160 30 units MAPA</th>
<th>V160 100 units MAPA</th>
<th>V160 250 units Placebo</th>
<th>V160 30 units Placebo</th>
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<tr>
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<td>12 (86)</td>
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<td>9 (69)</td>
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<td>1 (7)</td>
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<td>2 (15)</td>
<td>4 (40)</td>
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<tr>
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<td>9 (69)</td>
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<tr>
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<td>6 (46)</td>
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<tr>
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<td>4 (40)</td>
<td>5 (46)</td>
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Abbreviations: AE, adverse event; MAPA, Merck aluminum phosphate adjuvant.
acquisition of the data. M. P. C., R. R., and H. T.: Acquisition of the data. M. A.-I.: Acquisition of the data, interpretation of the results. T. M. F.: Conception, design or planning of the study, analysis of the data, interpretation of the results, drafting of the manuscript. O. B.: Conception, design or planning of the study, analysis of the data, interpretation of the results. D. W.: Conception, design or planning of the study, interpretation of the results. A. F., T. C., K. B., and G. T.: Conception, design or planning of the study. R. D.: Analysis of the data, interpretation of the results, drafting of the manuscript. All authors: Critically reviewing or revising the manuscript for important intellectual content and final approval.

All authors provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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