

# **Allogeneic Adipose-derived Mesenchymal Stem Cells for treatment of Moderate to Severe Psoriasis vulgaris (ADMSP): a study protocol for an open-label, uncontrolled clinical trial**

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## ABSTRACT

**Background:** Psoriasis is considered as an incurable immune-mediated inflammatory skin disease. A recent breakthrough in cell therapy is expected to be a new treatment for psoriasis. There have been some pioneer case reports demonstrated that Adipose-derived Mesenchymal Stem Cells (AD-MSCs) have therapeutic potential against psoriasis, which reveals it is necessary to gain more evidence for its safety and efficacy. Therefore, we introduce the protocol of a new clinical trial (ADMSP), the study on intervention using AD-MSCs as a new treatment.

**Method/Design:** ADMSP is an open-label, uncontrolled study. The aim of this study is to determine the safety and efficacy of AD-MSCs for moderate to severe psoriasis. It is anticipated to recruit seven participants. Patients will be received intravenous injection of AD-MSCs once a month. Safety is assessed using incidence of Adverse Events(AEs) and Serious Adverse Events (SAEs). Efficacy is assessed via the proportion of the improvement of PASI (Psoriasis Area and Severity Index), relapse rate in treatment period, changes in PASI score and BSA, as well as DLQI. The assessments are conducted at baseline (2 week prior to treatment) and 1 ,2, 3 months following investigational intervention.

**Discussion:** This is a trial of AD-MSCs for the patients with moderate to severe psoriasis. Once this trial is successful, it is expected to be accelerated for its application to a larger cohort of patients in the context of multicenter clinical trials.

**Clinical Trial Registration:** Clinical Trials.gov, NCT03265613, Registered 25 August 2017, <https://register.clinicaltrials.gov/>;

**Keywords:** Adipose-derived mesenchymal stem cells, Psoriasis, Protocol, clinical trial

## BACKGROUND

Psoriasis is considered as an incurable immune-mediated inflammatory disorder that occurs in 2 to 3% of the global population<sup>[1]</sup>. Its cutaneous manifestation characterized by disfiguring scaling, and erythematous plaques. Psoriasis is associated with both a physical and psychological burden<sup>[2]</sup> which could cause significant quality of life issues<sup>[3]</sup>. Mild to moderate psoriasis can often be managed with topical agents, while patients with moderate to severe psoriasis should need phototherapy or systemic therapy. The pathology of psoriasis involves complex pathogenic interactions between the innate and adaptive immune system. T cells are considered to play a major role in the development of psoriasis and T-cell targeting immunotherapy is now considered to be a possible strategy for the treatment of this disease<sup>[4]</sup>. Unfortunately, there is still no ideal management for psoriasis. Despite the availability of several therapies, many patients do not have an adequate response, or have treatment-related toxic effects<sup>[5]</sup>. This will add more urgent need to find alternative management strategies.

Cell transplantation are currently being developed and explored. Complete remission of psoriasis has also been observed after autologous hematopoietic stem cell transplantation (HSCT)<sup>[6]</sup>. Adult mesenchymal stem cells (MSCs), including adipose-derived mesenchymal stem cells (AD-MSCs) are considered a promising tool for cell therapy especially for treating inflammatory and autoimmune diseases due to their immunomodulatory capacity and paracrine effects through trophic factors with antifibrotic, antiapoptotic, or pro-angiogenic properties<sup>[7-8]</sup>. Studies have shown that MSCs mediate the activation and function of various cells of the innate and adaptive immune systems, including macrophages, neutrophils, natural killer cells, dendritic cells, T lymphocytes, and B lymphocytes<sup>[9]</sup>. The proinflammatory cytokine interferon- $\gamma$  (IFN- $\gamma$ ), alone or in combination with tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-1 $\alpha$ , or IL-1 $\beta$ , induces MSC to secrete various chemokines and inducible nitricoxide synthase (iNOS), which mediate immunosuppressive activity<sup>[10]</sup>. Due to these immunoregulatory properties, MSCs are being explored in a number of autoimmune diseases including Crohn's disease<sup>[11]</sup>, system lupus erythematosus (SLE)<sup>[12]</sup>,

graft-versus-host disease (GVHD)<sup>[13-14]</sup>, and rheumatoid arthritis (RA)<sup>[15]</sup>. Recently, several clinical trials have been registered at the NIH ClinicalTrials.gov database utilizing umbilical cord derived MSCs for psoriasis<sup>[16]</sup>. More and more case reports have suggested the clinical potential of MSCs transplantation following immunomodulation for psoriasis patients<sup>[17-19]</sup>.

Compared with other types of MSCs derived from bone marrow(BM) or umbilical cord matrix(UCM), AD-MSCs blocked the T cell activation process in an earlier phase than BM-MSCs or UCM-MSCs, yielding a greater proportion of T cells in the non-activated state<sup>[20]</sup>. Besides, AD-MSCs are easily accessible and abundant (about  $1 \times 10^5$  AD-MSCs per gram of fat<sup>[21]</sup>). The low immune privilege of AD-MSCs<sup>[22]</sup> supports the feasibility of allogeneic treatments without the requirement of suppression of host immunity. One of the case reports utilized autologous AD-MSCs for one patient with psoriasis vulgaris (PV) and another with psoriatic arthritis (PA) and found that autologous MSCs for the treatment of psoriasis were safe and effective<sup>[18]</sup>, which warrants clinical studies to investigate the long-term safety and efficacy of this approach. The recent case report of another patient with psoriasis using Stromal vascular fraction (SVF) collected from adipose tissue to treat psoriasis with a rapid reduction of PASI one month after intravenous implantation. The patient did not complain any safety concerns and did not experience any severe adverse events<sup>[19]</sup>, these case reports demonstrated that AD-MSCs may be a feasible new treatment option. The results of another research suggested that the immune inflammation suppression of AD-MSCs derived from healthy donors was stronger than those derived from patients<sup>[23]</sup>. However, no clinical use of allogenic AD-MSCs for this indication has been reported so far to our knowledge. We have developed a standardized protocol that we believe will provide evidence for clinical use of allogenic human AD-MSCs on psoriasis patients. Our main hypothesis is that allogenic AD-MSCs can be delivered to the targeted areas in vivo where T cells had been activated and proliferated with the increased anti-inflammatory paracrine activity to inhibit inflammation and have a therapeutical effect on psoriasis.

The aim of this trial is to investigate the hypothesis that intravenous injection of

allogenic AD-MSCs is safe, feasible, and well tolerated as a therapeutic modality in moderate to severe psoriasis patients. To establish a rigid basis for future efficacy trials, we are reporting the first pilot trial protocol of a nonrandomized, unicentric, open-label, uncontrolled clinical trial of intravenous infusion of allogenic AD-MSCs in patients with moderate to severe psoriasis.

## **METHODS**

### **Study design**

The study is a single-arm trial, and will be performed in accordance with the Academic Board of Guangdong Provincial Hospital of Chinese Medicine(GPHCM) and Ethics Committee of GPHCM and with policies of CFDA and National Health Commission of the People's Republic of China(NHCPRC). The original protocol has been approved by the Ethics Committee of GPHCM (Ethics Statement No: S2017-01-01) and both of CFDA and NHCPRC approved the protocol (No.CMR-20170220-1001. [http://114.255.123.14/project\\_detail.jsp?id=16](http://114.255.123.14/project_detail.jsp?id=16)). The ethics committee will track the progress of the trial every six months. Both of CFDA and NHCPRC will audit the trial every year. The Guangdong International Clinical Research Center of Chinese Medicine performs trial monitoring and has no competing interests.

### **Settings and Patients**

The study will be undertaken in the dermatology Department of GPHCM, in Guangzhou, China. The entire trial consists of an initial assessment, a two week run-in period (week -3) and one week for cell culture for AD-MSCs(week -1), a 12-week treatment phase (week 0 to week 12)(Figure 1). Recruitment will be through poster advertisement, newspaper advertisement, and Internet advertisement. Participants might also be invited to contact trial coordinators by their treating physician (general practitioner, dermatologist or immunologist). Seven participants (with both genders) will be included in the study after providing written informed consent. Each patient will also sign the informed consent to agree to the anonymous

usage of their biological specimen for research purposes according to the Declaration of Helsinki. Patients will be screened twice before and after culture for AD-MSCs and will undergo the stem cell therapy procedure using our protocol (Fig. 1 and Table 1).

### **Eligibility criteria**

#### Inclusion Criteria

1. Moderate to severe psoriasis vulgaris ( PASI > 10 or BSA >10% )
2. 18 to 65 years old
3. Written/signed informed consent

#### Exclusion Criteria

1. Guttate psoriasis, inverse psoriasis or exclusively associated with the face
2. Acute progressive psoriasis, and erythroderma tendency
3. Current (or within 1 year) pregnancy or lactation
4. Current significant anxiety or depression with the Self-rating Anxiety Scale (SAS) > 50 or the Self-rating Depression Scale (SDS) > 53, or with other psychiatric disorders
5. With history of primary cardiovascular, respiratory, digestive, urinary, endocrinologic and hematologic diseases, which can't be controlled through ordinary treatments. Those who with malignant diseases, infections, electrolyte imbalance, acid-base disturbance. Patients with clinical test results listed below: abnormal serum calcium level (  $Ca^{2+}$  > 2.9 mmol/L or < 2 mmol/L);AST or ALT 2 times more than normal upper limit; Creatinine and cystatin C more than normal upper limit; Hemoglobin elevates 20g/L more than normal upper limit,or hemoglobin reduction to anemia; Platelet count less than  $75.0 \times 10^9/L$ ; White blood cell less than  $3.0 \times 10^9/L$ ; Or any other abnormal laboratory test results, assessed by investigators, that are not suitable for this clinical study.
6. Patients with malignant tumors, or when they were enrolled with abnormal tumor markers or with other organ dysfunction
7. Allergy to anything else ever before;

8. Current registration in other clinical trials or participation within a month;
9. Topical treatments (i.e. corticosteroids or retinoic acid or Vitamin D analogs ) within 2 weeks; systemic therapy or phototherapy (ultraviolet radiation B,UVB) and psoralen combined with ultraviolet A (PUVA) within 4 weeks; biological therapy within 12 weeks;
10. Medical conditions assessed by investigators, that are not suitable for this study.

### **Preparation of AD-MSCs**

Cell source for AD-MSCs used in this trial is obtained by extracting adipose tissues from subcutaneous fat of the abdominal wall of healthy volunteers in Department of Plastic surgery, Peking Union Medical College Hospital. Donor suitability will be ensured by a study of medical history plus laboratory tests to exclude the transmission of infectious agents (human immunodeficiency virus, hepatitis B, hepatitis C, syphilis). Besides, Electrocardiogram and X-rays of chest , bone marrow morphology and routine blood test will also be tested to ensure donors' health and suitability.

Donors should be in the age of 18-35 for females and 18-40 for males. Healthy donors will sign informed consent before donation. The adipose tissues will be brought to the Center of Excellence in Tissue Engineering, Institute of Basic Medical Science, and the following processes will be performed in a closed operation system. 50-100ml adipose tissues will be placed in 50 mL centrifuge tube under aseptic condition, and added by fat suction fluid with 800 rpm/min centrifugation for 3 min. The upper adipose tissue will be absorbed and rinsed with normal saline, and centrifuged for 5 min for 800 rpm/min. Upper layer fat will be kept after 2 times centrifugation.

Enzyme dissolution procedure of the adipose tissue, using collagenase digestive solution under agitation in a 37°C constant temperature shaking bed for 30 min until there is no big block tissues. The cell suspension was filtered into a new centrifuge tube with 100µm cell sieve and centrifuged for 10 min. The supernatant and debris will be removed and cells will be precipitated plus to separate the stromal cell fraction (pellet) from adipocytes. The cells will be suspended in a complete culture medium, and be incubated in a culture bottle with a density of about  $1 \times 10^6$  / mL at 37°C with

5% CO<sub>2</sub>. After 24 h, nonadherent cells will be removed by changing the medium. The culture medium is replaced 2 times a week. To prevent spontaneous differentiation, cultures will be maintained at subconfluent levels (<80% confluence) and will then be designated as passage zero. In this trial, culture expansion will be limited to five passages to maintain genetic stability according to the guidelines of CFDA.

Before cell transplantation, cells will be washed in sterile saline, and viability will be evaluated for quality control according to Standards for Stem Cell formulations with reference to the guidelines of CFDA and NHCPRC<sup>[24]</sup>. Cells will be suspended in 100ml physiological saline. All procedures for cell processing are carried out according to Good Manufacturing Practice using aseptic procedures and disposable sterile single-use supplies for all product contact steps. The quality control of the AD-MSCs have been accredited by National Institutes of Food and Drug Control.

### **Surface Phenotype Characteristics of AD-MSCs**

AD-MSc surface markers will be characterized using a flow cytometer (Becton Dickinson, FACS Aria II ) after labeling with antibodies against the human clusters of differentiation: CD29、CD44、CD105、CD73、CD90 (High expression, >95%), CD34、CD45(no expression), HLA-ABC ( >95%) HLA-DR (less expression, <5%).

### **Intervention**

On the day when AD-MSCs is manufactured, the cell product will be administered to the subject. Participants will receive AD-MSCs by intravenous injection at a dose of 0.5 million cells/kg with a rate of 30 drops per minute in the inpatient dermatology department of GPHCM at week 0, week 4, week 8 with a duration for 12 weeks. Hospitalization observation is required until 48 hours after injections. The basic conditions of the vital signs such as heart rate, blood pressure, respiration, oxygen saturation will be monitored and recorded every 30 minutes. During the infusion, ECG monitoring will also be recorded every 30 minutes. All of the above indicators monitored will be recorded continuously for 5 hours after injection to ensure the safety of participants.

**Criteria for discontinuing the intervention**

1. During the treatment period, if the disease condition is suddenly increased, and the rash develop rapidly, exceeding 90% of the body surface area or psoriasis vulgaris transforms into new generalized pustular or psoriatic arthritis or psoriasis erythrodermic.
2. The disease rebound (the condition becomes worsen after improvement (PASI-50), in addition, PASI score increases more than 125% of baseline) after at least one AD-MSCs injection within 30 days.
3. Primary severe diseases such as active therioma, decompensation of liver cirrhosis, or ematopoietic system were found during the observation period.
4. Drug side effects, such as allergic reactions, shock, pulmonary embolism, were observed.
5. Diseases such as acute abdomen, trauma need to be treated surgically during the observation period.
6. Adverse events were found with myocardial infarction or cerebrovascular events or severe complication during the treatment period.
7. Patients who are not able to maintain an appropriate follow-up schedule
8. Patients who opt to withdraw

**Rescue and concomitant treatment**

Urea ointment is used as the basic concomitant treatment in the run-in and follow-up period, according to doctors' opinion. In case patient with a serious itch, cetirizine hydrochloride (10mg/day) is to be a rescue drug follows the doctor's advice. Besides, participants will receive rescue in emergency according to guidelines when complications such as allergic shock, severe infection or pulmonary embolism happen to come out.

**Outcomes**

Primary outcome (Safety assessments)

Incidence, relatedness, and severity of treatment-emergent suspected unexpected

serious adverse reactions, serious adverse events (SAEs), and adverse events (AEs) will be documented at each visit throughout the study. All AEs reports will be recorded and assessed the causal relationship with the treatment by investigators. Clinically relevant AEs (ie, grades 3-5) related to AD-MSCs administration will be considered dose-limiting toxicity (DLTs)<sup>[25]</sup>. Intensity of AEs will be assessed following the Common Terminology Criteria for AEs, V. 5.0, of the National Cancer Institute, ranging from 1 to 5<sup>[26]</sup>.

Laboratory tests(see Table 1 and 2 ), vital signs, and physical examinations of the patients will be assessed systematically. A 48-hours safety period will be implemented after each injection. All abnormal changes from baseline of lab test will be evaluated by investigators and will be monitored by the Data Monitoring Committee (DMC) from GPHCM.

#### Secondary outcomes (Efficacy assessments)

Secondary efficacy endpoints will be assessed by measuring changes of PASI (Psoriasis Area and Severity Index), Body Surface Area (BSA) of involved lesions, Pruritus Scores on the Visual Analogue Scale (VAS) and DLQI (Dermatology Life Quality Index) from baseline to week 12. The proportion of the improvement of PASI will be also assessed, especially for PASI-50 and PASI-75(the proportion of patients who achieve at least 50% or 75% improvement in PASI score from baseline to week 12).

Standard photos will be taken by doctors to record subjects' psoriatic area and severity and to assess PASI score.

#### **Follow-Up**

All patients will be followed regularly by telephone call every week and will be evaluated by PASI, BSA and routine laboratory tests every month according to our clinical schedule(Table 1). Meanwhile patients will be required to keep a daily record of the skin condition and the concomitant drug if they need to use. At the end of the study, there will be a follow-up of one year by telephone call or via face-to-face

interviews.

### **Data management and quality control**

The data collected in this trial comprises of information recorded in case report forms (CRF) and information on the DLQI scale. Participants will record further daily and weekly data in a home data diary, to be collected by researchers at subsequent assessment or review appointments to check adherence. When every visit is completed, data will be entered using the double entry method. Both paper and electronic versions of the CRF will be kept in the secure research archives at GPHCM for 30 years after the trial finishes. All researchers will be given complete good clinical practical training and will get a certification before the trial conducts. To ensure the quality of the trial, all of the researchers will be in accordance with a standard operating procedures (SOPs) for the trial according to Good Clinical Practice. All of the staff will be trained with the protocol and SOPs, and they will drill it for twice before the trial begins.

### **Statistical analysis**

Data analyses will be processed with SPSS Windows Version 18.0 (IBM Corp., Armonk, NY). Multiple imputation will be used to evaluate data with an intention-to-treat analysis. Continuous data will be presented as means and standard deviations. Categorical data will be presented as absolute frequencies or relative percentages. Primary and secondary endpoints will be observed for each patient against the baseline values. Safety will also be analyzed for each patient. If the number of adverse reactions is more, we should analyze the relationship with the duration of medication, baseline characteristics and so on. A p value < 0.05 will be considered as statistically significant.

### **Monitoring**

The Data Monitoring Committee(DMC) from GPHCM which is composed of experts with relevant professional qualifications, familiarity with the clinical research and

experienced with data and safety monitoring, will be responsible for assessing the safety data and the critical efficacy outcomes independently, in a timely and effective manner. By examining the data and progress reports submitted by researchers, the DMC may make written recommendations or decide whether to suspend the study for the following reasons: 1) extremely significant curative effect 2) unacceptable safety risk 3) ineffectiveness, etc. The committee could also recommend changes to ongoing studies, such as lowering doses and removing intervention groups that could present unacceptable safety risks.

## **DISCUSSION**

Although some case reports had been reported that MSCs were effective for psoriasis and more and more clinical trials had been registered for MSCs as a new therapy, currently, the application status of MSCs as treatment modalities in psoriasis is still in its infancy and remains exploratory. To our knowledge, the trial is the first attempt to evaluate the safety and efficacy of AD-MSC in patients with moderate to severe psoriasis. Owing to the immunomodulation property of stem cells, they have been used to treat GVHD, and autoimmune diseases such as refractory systemic lupus erythematosus<sup>[27]</sup>, and rheumatoid arthritis<sup>[28]</sup>. Expanded allogeneic adipose-derived mesenchymal stem cells were proven to have therapeutic treatment for complex perianal fistulas in Crohn's disease<sup>[29]</sup>. A study showed that mesenteric injection of AD-MSCs in experimentally-induced colitis in rats could reduce interleukin (IL)-17A expression, while could increase IL-10 production and regulate the balance of the Th17/Treg cell which is also the main pathogenesis of psoriasis<sup>[30]</sup>. It indicated that AD-MSCs injection might be a promising approach to regulate the balance of the Th17/Treg cell and might be a potential therapy for psoriasis. Therefore, if the trial is successful, it could be accelerated for its application to a larger cohort of patients in the context of multicenter clinical trials. Larger multicenter placebo-controlled clinical trials are sorely needed in order to prove efficacy.

**Subject screening**

Stem cell therapy is a special intervention and we will have to screen participants for twice because it needs time for tissue collection and cell culture. For the purpose of safety, participants will be screened the second time just before receive injection because sometimes the severity of the disease will get worse when participants happen to have a cold in several days. If changes in a subject's condition are anticipated during the manufacturing period, appropriate screening at the start of the administration, as well as at the enrollment should be established.

**Safety measures for injection**

So far as we know, it is the first exploratory research. There are many unknown circumstances. In order to ensure the safety of the subjects, every participant will receive injection in the special hospital ward. All of the rescue equipment will be available on the ward. A research nurse or a doctor will stay with the participant to see if there is an emergency for the patient during injection. All of the investigators will be trained on how to deal with emergencies or complications occurred after injection. They keep in touch with doctors in the intensive care unit(ICU). If the condition is getting worse, the participant will be transferred to ICU as soon as possible to get life support and further treatment.

Attention should be paid to possible complications of stem cell injection, such as allergic shock, severe infectious, or pulmonary embolism due to the transplantation of cells. In order to minimize the damage from complication, we trained investigators and all of the doctors on duty with the treatment guidelines about these complications before the trial begins. According to the guidelines, we have developed a flow chart for the treatment of these complications so that each doctor on duty can follow the procedure in the course of rescue.

**Administration dose and time point**

In our protocol, the administration dose is determined based on prior clinical trials and case reports. It was reported that under the dosage of AD-MSCs from 0.5 million

cells/kg -3 million cells/kg<sup>[18]</sup>, patients could benefit from stem cells after 3 intravenous injections. However, the first pilot study is of major importance and represent the first hamper that should be overcome. For full consideration of safety, we choose 0.5 million cells/kg as our treatment dosage and three injections in 4 weeks interval in the protocol.

### **Limitations**

Since it is the first trial to explore this novel therapeutic option, there is still plenty of room for further technical improvements, development and widespread acceptance and accessibility. The sample size is limited. Whether the administration dosage or time point is suitable and whether the trial procedures is feasible are still under exploration. After we finish the trial, we will find more problems to solve and modify the protocol to be more acceptable and feasible.

### **Trial status**

The trial is currently recruiting patients in Guangdong Provincial hospital of Chinese Medicine, China.

### **List of abbreviations**

AD-MSCs: Adipose-derived Mesenchymal Stem Cells  
AEs: Adverse Events  
AFP: Alphafetoprotein  
BM: Bone Marrow  
BSA: Body Surface Area  
CEA: Carcinoembryonic Antigen  
CFDA: China Food and Drug Administration  
CRF: Case Report Form  
DLT: Dose-limiting Toxicity  
DLQI: Dermatology Life Quality Index  
DMC: Data Monitoring Committee  
ECG: Electrocardiogram  
eGFR: Estimated Glomerular Filtration Rate  
GPHCM: Guangdong Provincial Hospital of Chinese Medicine  
GVHD: Graft-Versus-Host Disease  
HDL: High Density Lipoprotein  
ICU: Intensive Care Unit

IFN- $\gamma$ : interferon- $\gamma$   
iNOS: inducible Nitricoxide Synthase  
LDL: Low Density Lipoprotein  
MSCs: Mesenchymal Stem Cells  
NHCPRC: National Health Commission of the People's Republic of China  
PA: Psoriatic Arthritis  
PV: Psoriasis Vulgaris  
RA: Rheumatoid Arthritis  
SLE: System Lupus Erythematosus  
SVF: Stromal Vascular Fraction  
TNF- $\alpha$ : tumor necrosis factor- $\alpha$   
PASI: Psoriasis Area and Severity Index  
PUVA: psoralen combined with ultraviolet A  
UCM: Umbilical Cord Matrix  
UVB: ultraviolet radiation B  
VAS: Visual Analogue Scale

### **Ethics approval and consent to participate**

This research protocol had been reviewed and approved by Ethics Committee of GPHCM (Ethics Statement No: S2017-01-01). The Biological Resource Centre of GPHCM approved the biobank procedure. Written informed consent will be given by participants. The informed consent forms for participation in clinical trial and the biobanking part are separated. The results will be disseminated to the public through conference presentations and open access journals.

### **Consent for publication**

Not applicable.

### **Availability of data and material**

The datasets generated or analyzed during this study are not publicly available to ensure patient privacy, but available from the corresponding author on reasonable request.

### **Competing interests**

None declared

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### **Authors' contributions**

DNY, JWD prepared the initial draft of the manuscript. DNY, JWD and ZYH developed the CRF. CJL, ZHW designed the trial and had reviewed all study documents and processes. YH, XSC, HYL, YHY, QH, RCZ contributed to the development of the study protocol. All authors have comNational Health Commission of the People's Republic of Chinamented upon drafts of the manuscript and have given approval to the final version.

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