



February 4, 2021

Nikki Bratcher-Bowman
Acting Assistant Secretary for Preparedness and Response
Office of the Assistant Secretary for Preparedness and Response
Office of the Secretary
U.S. Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Dear Ms. Bratcher-Bowman:

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19 (the virus was later named SARS-CoV-2).¹ On March 27, 2020, on the basis of such determination, the Secretary of HHS declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act, subject to the terms of any authorization issued under that section.²

On August 23, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the emergency use of COVID-19 convalescent plasma for the treatment of hospitalized patients with Coronavirus Disease 2019 (COVID-19), pursuant to Section 564 of the Act.³ On November 30, 2020, FDA reissued the August 23, 2020, Letter of Authorization to add a test acceptable to be used in the manufacture of COVID-19 convalescent plasma.⁴

Having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2)(C) of the Act (21 U.S.C. § 360bbb-3(g)(2)(C)), FDA is again reissuing the Letter of Authorization in its entirety with revisions to: (1) include updates based on data from additional clinical trials; (2) clarify that the authorization is limited to use of only high titer

¹ U.S. Department of Health and Human Services (HHS). *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*. February 4, 2020.

² HHS. *Emergency Use Authorization Declaration*. 85 FR 18250 (April 1, 2020).
<https://www.govinfo.gov/content/pkg/FR-2020-04-01/pdf/2020-06905.pdf>.

³ Additional information about this EUA can be found on the FDA website at <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs>.

⁴ The November 30, 2020, reissuance added the Mount Sinai COVID-19 ELISA IgG Antibody Test as an acceptable test to be used for the purpose of qualifying high and low titer COVID-19 convalescent plasma in the manufacture of COVID-19 plasma.

COVID-19 convalescent plasma in hospitalized patients early in the course of disease and those hospitalized with impaired humoral immunity; (3) add the Abbott SARS-CoV-2 IgG test (ARCHITECT and Alinity i platforms), Beckman Coulter Access SARS-CoV-2 IgG test, EUROIMMUN Anti-SARS-CoV-2 ELISA (IgG) test, GenScript cPass SARS-CoV-2 Neutralization Antibody Detection Kit test, Kantaro COVID-SeroKlir test, Roche Elecsys Anti-SARS-CoV-2 S test, and Siemens ADVIA Centaur SARS-CoV-2 IgG (COV2G) test as acceptable tests to be used for the purpose of qualifying high titer COVID-19 convalescent plasma in the manufacture of COVID-19 convalescent plasma; and (4) change the cutoff of the Ortho VITROS Anti-SARS-CoV-2 IgG test from $S/C \geq 12.0$ to $S/C \geq 9.5$ for qualification of COVID-19 convalescent plasma as high titer.

COVID-19 convalescent plasma is human plasma collected from individuals whose plasma contains anti-SARS-CoV-2 antibodies, and who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15) and qualifications. It is an investigational product and is not currently approved or licensed for any indication.

The initial issuance of this EUA for COVID-19 convalescent plasma was based on review of historical evidence using convalescent plasma in prior outbreaks of respiratory viruses, certain preclinical evidence, results from small clinical trials of convalescent plasma conducted during the current outbreak, and data obtained from the National Convalescent Plasma Expanded Access Protocol (EAP) sponsored by the Mayo Clinic.⁵

Following the August 23, 2020 authorization, additional studies, including randomized, controlled trials, have provided data to further inform the safety and efficacy of COVID-19 convalescent plasma, and further characterize product attributes and patient populations for its use. Based on assessment of these data, potential clinical benefit of transfusion of COVID-19 convalescent plasma in hospitalized patients with COVID-19 is associated with high titer units administered early in the course of disease.⁶ Transfusion of COVID-19 convalescent plasma in hospitalized patients late in the course of illness (e.g., following respiratory failure requiring intubation and mechanical ventilation) has not been associated with clinical benefit. These considerations may be different in patients with suppressed or deficient humoral immunity.

Therefore, this EUA is being revised to authorize only the use of high titer COVID-19 convalescent plasma, for the treatment of hospitalized patients with COVID-19, early in the disease course. The related fact sheets are revised accordingly. The use of low titer COVID-19 convalescent plasma is no longer authorized under this EUA.

⁵ A national expanded access protocol (EAP) sponsored by the Mayo Clinic was established in April 2020 and enrolled >100,000 subjects. The EAP discontinued enrollment in August 2020, following the issuance of the EUA for the emergency use of COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. The goal of this uncontrolled, single-arm study was to provide access to COVID-19 convalescent plasma in hospitalized subjects with severe or life-threatening COVID-19 or judged by the treating provider to be at high risk of progression to severe or life-threatening disease.

⁶ Based on what is known about the typical course of illness and kinetics of the humoral immune response in COVID-19, for most hospitalized patients, early in the course of disease likely represents prior to respiratory failure requiring intubation and mechanical ventilation. The therapeutic window may be longer when CCP is administered to patients with clinical or laboratory evidence of impaired humoral immunity.

It is reasonable to believe that the known and potential benefits of high titer COVID-19 convalescent plasma outweigh its known and potential risks for the treatment of patients hospitalized with COVID-19 early in the disease course.⁷

COVID-19 convalescent plasma should not be considered a new standard of care for the treatment of patients with COVID-19. Given that the clinical evidence supporting this EUA remains limited, data from additional randomized, controlled trials are needed. Ongoing clinical trials of COVID-19 convalescent plasma should not be amended based on the issuance of this updated EUA; providers are encouraged to enroll patients in those trials.

Having concluded that the criteria for issuance of this authorization under 564(c) of the Act are met, I am authorizing the emergency use of high titer COVID-19 convalescent plasma for treatment of hospitalized patients with COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of high titer COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19 when administered as described in the Scope of Authorization (Section II) meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause COVID-19, a serious or life-threatening disease or condition, including severe respiratory illness, in humans infected by this virus;
2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that high titer COVID-19 convalescent plasma may be effective in treating COVID-19, and that, when used under the conditions described in this authorization, the known and potential benefits of high titer COVID-19 convalescent plasma when used to treat COVID-19 outweigh the known and potential risks of the product; and
3. There is no adequate, approved, and available alternative to the emergency use of high titer COVID-19 convalescent plasma for the treatment of COVID-19.^{8,9}

II. Scope of Authorization

I have concluded, pursuant to section 564(d)(1) of the Act, that the scope of this authorization is limited to the use of the authorized high titer COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19, early in the course of disease, and those hospitalized

⁷ Information derived from ongoing clinical trials of COVID-19 convalescent plasma (particularly randomized controlled trials), as well as clinical trial results from studies of other investigational medical products to treat COVID-19, will continue to inform the risk-benefit assessment for this EUA.

⁸ At the time of reissuance of this letter of authorization, one drug had been approved by FDA for the treatment of certain hospitalized patients with COVID-19 and was available. However, the adequacy criterion was not met.

⁹ No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

with impaired humoral immunity. The emergency use of the authorized high titer COVID-19 convalescent plasma under this EUA must be consistent with, and may not exceed, the terms of this letter, including the scope and the conditions of authorization set forth below.

The Authorized COVID-19 Convalescent Plasma (Product Description):

I am authorizing the use of high titer COVID-19 convalescent plasma, a biological product to be used for the treatment of hospitalized patients with COVID-19, early in the course of disease, and those hospitalized with impaired humoral immunity.

COVID-19 convalescent plasma is human plasma collected from individuals whose plasma contains SARS-CoV-2 antibodies and who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15) and qualifications. Under this EUA, authorized COVID-19 convalescent plasma will be obtained from registered or licensed blood establishments from donors in the United States or its territories in accordance with applicable regulations, policies, and procedures. Testing for relevant transfusion-transmitted infections (21 CFR 610.40) must be performed and the donation must be found suitable (21 CFR 630.30).

Plasma donations must be tested by registered or licensed blood establishments for anti-SARS-CoV-2 antibodies as a manufacturing step to determine suitability before release, using one of the tests listed below, as follows:

Tests Acceptable for Use in the Manufacture of High Titer COVID-19 Convalescent Plasma		
Manufacturer (listed alphabetically)	Assay	Qualifying Result
Abbott	SARS-CoV-2 IgG (ARCHITECT and Alinityi)	Index (S/C) \geq 4.5
Beckman Coulter	Access SARS-CoV-2 IgG	S/CO \geq 3.3
EUROIMMUN	Anti-SARS-CoV-2 ELISA (IgG)	Ratio \geq 3.5
GenScript	cPass SARS-CoV-2 Neutralization Antibody Detection Kit	Inhibition \geq 68%
Kantaro	COVID-SeroKlir, Kantaro Semi-Quantitative SARS-CoV-2 IgG Antibody Kit	Spike ELISA > 47 AU/mL
Mount Sinai	COVID-19 ELISA IgG	Spike ELISA titer \geq 1:2880
Ortho	VITROS Anti-SARS-CoV-2 IgG	S/C \geq 9.5
Roche	Elecsys Anti-SARS-CoV-2 S	\geq 132 U/mL
Siemens	ADVIA Centaur SARS-CoV-2 IgG (COV2G)	Index \geq 4.8

If a blood establishment is considering using a different test in manufacturing in order to qualify high titer COVID-19 convalescent plasma, they should contact the FDA Center for Biologics Evaluation and Research (CBER) to determine acceptability of the proposed test, which if accepted, would require an amendment to this EUA.

To be labeled as COVID-19 convalescent plasma under this EUA, units containing anti-SARS-CoV-2 antibodies must be labeled as high titer according to the results of the tests described above. Low titer units are no longer authorized for use under the conditions of this EUA.

Health care providers will administer the authorized high-titer COVID-19 convalescent plasma with anti-SARS-CoV-2 antibodies according to standard hospital procedures and institutional medical and nursing practices. Clinical dosing may first consider starting with one high titer COVID-19 convalescent plasma unit (about 200 mL), with administration of additional high titer COVID-19 convalescent plasma units based on the prescribing physician's medical judgment and the patient's clinical response.

High titer COVID-19 convalescent plasma is authorized to be accompanied by the following product-specific information pertaining to emergency use, which is required to be made available to health care providers and patients respectively:

- Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of COVID-19 Convalescent Plasma for Treatment of COVID-19 in Hospitalized Patients.
- Fact Sheet for Patients and Parents/Caregivers: Emergency Use Authorization (EUA) of COVID-19 Convalescent Plasma for Treatment of COVID-19 in Hospitalized Patients.

Changes to the authorized Fact Sheets may be requested by the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) and are authorized to be made in consultation with, and with concurrence of, the Office of Blood Research and Review (OBRR)/Center for Biologics Evaluation and Research (CBER), Preparedness and Response Team (PREP)/Office of the Center Director (OD)/CBER, and Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS)/Office of the Commissioner (OC), as appropriate.

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of high titer COVID-19 convalescent plasma, when used for the treatment of hospitalized patients with COVID-19 early in the course of disease, and those hospitalized with impaired humoral immunity, and used in accordance with this Scope of Authorization (Section II), outweigh its known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that COVID-19 convalescent plasma may be effective for the treatment of hospitalized patients with COVID-19 early in the course of disease, and those hospitalized with impaired humoral immunity, when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that COVID-19 convalescent plasma (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of your product under an EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), high titer COVID-19 convalescent plasma is authorized for the treatment of hospitalized patients with COVID-19 early in the disease course, and those hospitalized with impaired humoral immunity as described in the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to section 564 of the Act, I am establishing the following conditions on this authorization:

ASPR

- A. ASPR will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, registered or licensed blood establishments, hospitals, health care providers) involved in distributing or receiving authorized COVID-19 convalescent plasma. ASPR will provide to all relevant stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized accompanying materials (i.e., Fact Sheets).
- B. ASPR may request changes to this authorization, and such changes may be permitted without amendment of this EUA upon concurrence of OBRR/CBER, PREP/OD/CBER, and OCET/OCS/OC.
- C. ASPR may request changes to the authorized Fact Sheets for high titer COVID-19 convalescent plasma, and such changes may be permitted without amendment of this EUA upon concurrence of OBRR/CBER, PREP/OD/CBER, and OCET/OCS/OC.
- D. ASPR will report to FDA serious adverse events and all medication errors associated with the use of the authorized COVID-19 convalescent plasma that are reported to ASPR, or of which ASPR otherwise becomes aware, during the pandemic.
- E. ASPR will make available to FDA upon request any records maintained in connection with this EUA.

Registered or Licensed Blood Establishments

- F. Registered or licensed blood establishments will ensure that the authorized COVID-19 convalescent plasma, accompanied with the authorized labeling (i.e., Fact Sheets), is distributed to hospitals consistent with the terms of this letter, and that such hospitals are aware of the letter of authorization.
- G. Registered or licensed blood establishments will ensure that appropriate storage and cold chain is maintained. The authorized COVID-19 convalescent plasma should be frozen after collection and stored at -18°C or colder. Once thawed, it can be refrigerated for up to 5 days prior to patient transfusion.
- H. Through a process of inventory control, registered or licensed blood establishments will maintain records regarding distribution of the authorized COVID-19 convalescent plasma (i.e., donor records, quantity, receiving site, receipt date).

- I. Registered or licensed blood establishments will make available to FDA upon request any records maintained in connection with this EUA.

Hospitals to Whom the Authorized COVID-19 Convalescent Plasma Is Distributed, and Health Care Providers Administering the Authorized COVID-19 Convalescent Plasma

- J. Hospitals and health care providers receiving authorized COVID-19 convalescent plasma will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available to health care providers and to patients and caregivers, respectively, through appropriate means.
- K. The authorized COVID-19 convalescent plasma must be stored frozen at -18°C or colder. Once thawed and refrigerated, the authorized COVID-19 convalescent plasma must be used within 5 days for patient transfusion.
- L. Hospitals and health care providers administering COVID-19 convalescent plasma will track serious adverse events that are considered to be potentially attributable to COVID-19 convalescent plasma use and must report these to FDA in accordance with the Fact Sheet for Health Care Providers. Health care providers must maintain records and conduct a thorough investigation of adverse reactions after transfusion of convalescent plasma, and must report fatalities related to transfusion, as required under 21 CFR 606.170.
- M. Through a process of inventory control, hospitals will maintain records regarding the administered authorized COVID-19 convalescent plasma (e.g., donation identification number, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).
- N. Hospitals will ensure that any records associated with this EUA are maintained until notified by ASPR and/or FDA. Such records will be made available to ASPR, HHS, and FDA for inspection upon request.

Conditions Related to Printed Matter, Advertising, and Promotion

- O. All descriptive printed matter, advertising, and promotional materials relating to the use of the authorized COVID-19 convalescent plasma shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in Section 502(a) and (n) of the Act and FDA implementing regulations.
- P. No descriptive printed matter, advertising, or promotional material relating to the use of COVID-19 convalescent plasma may represent or suggest that such product is safe or effective.

- Q. All descriptive printed matter, advertising, and promotional materials relating to the use of COVID-19 convalescent plasma clearly and conspicuously shall state that:
- COVID-19 convalescent plasma has not been approved or licensed by FDA but has been authorized for emergency use by FDA under an EUA for the treatment of hospitalized patients with COVID-19; and
 - The emergency use of COVID-19 convalescent plasma is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated, or authorization revoked sooner.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

--/S/--

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures



CLINICAL MEMORANDUM

From: Carlos H. Villa MD PhD, Medical Officer, OBRR/DBCD/CRS

To: Nicole Verdun MD, Director, OBRR

Through: Orijei Illoh MD, Division Director, OBRR/DBCD
Wendy Paul MD, Deputy Division Director, OBRR/DBCD
Salim Haddad MD, Team Lead, OBRR/DBCD/CRS

Re: EUA 26382

Product: COVID-19 Convalescent Plasma

Sponsor: Assistant Secretary for Preparedness and Response (ASPR)
Office of Assistant Secretary for Preparedness and Response (ASPR)
U.S. Department of Health and Human Services (HHS)

EXECUTIVE SUMMARY

COVID-19 Convalescent Plasma (CCP) was granted Emergency Use Authorization (EUA) for the treatment of hospitalized patients with COVID-19 on August 23, 2020. At that time, the totality of the scientific evidence supported a determination that the use of CCP in hospitalized patients with COVID-19 met the “may be effective” standard for issuance of an EUA, and it was reasonable to consider that the known and potential benefits of CCP outweighed the known and potential risks for the authorized use.

Following the EUA, emerging evidence from randomized controlled trials has continued to inform this assessment. The available evidence indicates that 1) the use of low titer CCP in hospitalized patients no longer meets the evidentiary standard of “may be effective”, and 2) high titer CCP has not demonstrated benefit when administered late in the disease course in immunocompetent hospitalized patients.

Additional data from RCTs and observational studies support a determination that high titer CCP may be effective when administered early in the course of illness, particularly prior to the expected time of host antibody response. In patients with impaired humoral immunity, the potential therapeutic window may be prolonged. As RCT data continue to demonstrate that the risks of CCP do not exceed those observed with plasma transfusion in general, it is reasonable to believe that the known and potential benefits of use of high titer CCP outweigh the known and potential risks when used for the treatment of hospitalized patients with COVID-19, particularly early in the course of illness or in patients with impaired humoral immunity. Results from ongoing RCTs are expected to continue inform the optimal patient populations and product characteristics for efficacy of CCP in COVID-19.

Recommendation: The conditions of Emergency Use Authorization for CCP for the treatment of hospitalized patients with COVID-19 should be revised to exclude the use of low titer CCP. High titer CCP continues to meet criteria for Emergency Use Authorization for the treatment of hospitalized patients with COVID-19 early in the course of hospitalization. The letter of authorization and accompanying fact sheets should be revised to emphasize early administration of CCP in the absence of immunodeficiency or immunosuppression. Additional results from adequate and well-controlled trials will continue to be evaluated to further characterize the patient populations and product characteristics meeting EUA criteria.

Regulatory History

FDA issued an Emergency Use Authorization (EUA 26382) on August 23, 2020 for the use of COVID-19 Convalescent Plasma (CCP) for treatment of hospitalized patients with COVID-19. This authorization was based on the totality of the scientific evidence available at the time, which supported a determination that CCP met the “may be effective” criterion for issuance of an EUA and that the known and potential benefits of CCP outweighed the known and potential risks of CCP for the terms of the EUA. Considering the limited data from adequate and well-controlled randomized trials at the time of the issuance of the EUA, FDA noted in the August 23, 2020 Letter of Authorization that additional data from such trials remained necessary for a definitive demonstration of CCP efficacy and to determine the optimal product attributes and appropriate patient populations for use of CCP. Information derived from ongoing clinical trials of CCP, particularly randomized, controlled trials, as well as clinical trial results from studies of other investigational medical products to treat COVID-19, were expected to inform the continuing risk benefit assessment. The current proposed amendment to the EUA revises the conditions of authorization to reflect the accumulated evidence on the use of CCP in COVID-19.

Summary of Evidence Following the August 23, 2020 EUA

Randomized Controlled Trials (RCTs)

At the time of the issuance of the original EUA for CCP, results from two RCTs had been published or made publicly available[1, 2]. Both studies failed to demonstrate a significant benefit with CCP transfusion, but may have been underpowered due to early stopping either due to low enrollment[1] or to the presence of high antibody titers in subjects prior to transfusion[2]. Additionally, patients were treated relatively late in illness, at a median of 30 days[1] and 10 days[2] post symptom onset. Following issuance of the EUA for CCP, the results of several additional RCTs of CCP were published or made publicly available.

The PLACID study, conducted in India, did not observe a difference in progression to severe disease or death by 28 days in 235 patients receiving CCP and standard of care compared to 229 subjects randomized to standard of care alone (open label)[3]. At enrollment, subjects reported a median of 8 days of symptoms (IQR 6-11) and 83% had detectable neutralizing antibodies. A higher proportion of patients in the interventional arm showed resolution of shortness of breath and fatigue on day 7, and negative conversion of SARS-CoV-2 RNA at day 7 was higher in the intervention arm. Other secondary outcomes (including days of respiratory support) showed no significant differences. The findings of the trial may have been limited by the relatively low titers in the transfused plasma. Only 71.4% of participants received plasma with detectable neutralizing antibodies and donors had a median titer of 1:40 (IQR 1:30-1:80) compared to a median titer of 1:90 (IQR 1:30-1:240) in recipients at enrollment. While subgroup analyses based on titers and duration of symptoms did not demonstrate significant differences, these may have been underpowered to detect clinically important differences. For example, the subgroup analysis for those with symptoms for three days or less at enrollment was based on only 24 subjects and found a risk ratio for the composite outcome of 0.8 (95% confidence interval 0.2 to 3.1).

The PlasmAr study in Argentina, a double-blind placebo-controlled study of CCP in hospitalized patients with severe COVID-19, found no improvement at 30 days in clinical status or overall mortality with transfusion of 500 mL of CCP in 228 test subjects compared to 105 control subjects receiving a normal saline placebo[4]. Prior to transfusion of CCP, titers were measured using an ELISA assay for antibodies against the SARS-CoV-2 spike protein and receptor binding domain and showed a median titer of 1:3200 (IQR 1:800-1:3200). Based on the correlation of this assay with neutralization activity, these titers would be consistent with a classification of high titer under this EUA (ID50 neutralization titer >1:250). The median time from symptom onset to enrollment was 8 days (IQR 5-11) and 54% of subjects had detectable antibodies at baseline. The prespecified subgroup analyses failed to demonstrate credible subgroup effects but was limited by the relatively small subgroup size (for example, 39 subjects [17%] received the intervention within 72 hours of symptom onset). No significant differences in the overall incidence of adverse events were observed, and the most common infusion-related event was nonhemolytic febrile reactions.

The ConPlas-19 study in Spain observed a trend towards a survival benefit with administration of high titer CCP (median neutralization titer 1:292, IQR 238-451) to hospitalized patients with COVID-19, but the difference did not meet the prespecified statistical test for significance[5], and the study was stopped early due to diminished enrollment as the local number of cases dropped, resulting in a small number of events and limited statistical power. 81 patients were randomized to the study and reported a median of 8 days of symptoms (IQR 6-9) with 49.4% positive for anti-SARS-CoV-2 antibodies at enrollment. No significant differences were found in secondary endpoints, including time to improvement on an ordinal scale of severity, proportion of patients requiring high flow oxygen, non-invasive ventilation, or higher respiratory support, hospital length of stay, and days free from oxygen support.

A small randomized controlled trial of CCP in patients with severe COVID-19 compared to standard of care (n=40 per arm) found no significant clinical benefit in the overall population, although a post-hoc subgroup of patients younger than 67 years old demonstrated clinical benefit[6]. Plasma was tested for the presence of neutralizing antibodies using a surrogate neutralization assay, but further quantitative information on antibody content or titer was not provided. Another small randomized pilot study (n=20 per arm) found CCP transfusion to be safe but also did not observe differences in the primary outcome of mechanical ventilation compared to standard of care[7]. Prospective antibody titration was not performed.

The RECOVERY study in the United Kingdom, a large platform trial that has evaluated multiple COVID-19 therapies[8], included a comparison of CCP to standard of care. A January 15, 2021 statement from the RECOVERY trial chief investigators reported that enrollment in the CCP arm would be halted after the independent Data Monitoring Committee saw no convincing evidence that further recruitment would provide conclusive proof of worthwhile mortality benefit[9]. The preliminary analysis, based on 1873 reported deaths among 10,406 randomized patients, showed no significant difference in the primary endpoint of 28-day mortality. The results of the study have not been published at this time, and additional information on the timing of product administration relative to symptom onset, baseline patient antibody titers, and antibody titers in the transfused CCP will be important to further evaluate the findings.

In the outpatient setting, Libster et al reported the results of a randomized, double-blind, placebo-controlled trial of 250 mL of CCP versus saline placebo in 160 high risk adults (75 years or older, or 65 to 74 with at least one comorbidity (hypertension, diabetes, obesity, chronic renal failure, cardiovascular disease, and COPD)[10] with mild COVID-19 symptoms. The investigators used the same serologic assay used to qualify CCP in the PlasmAr study described above and used plasma from donors with a titer of 1:1000 or greater. The intervention was administered less than 72 hours after the onset of symptoms and the primary endpoint was progression to severe respiratory disease. While the trial was halted due to a local decrease in cases, at 76% of target enrollment, they observed a 48% relative risk reduction in development of severe respiratory disease within 15 days, with the primary outcome occurring in 25 of 80 subjects (31%) in the placebo arm, and 13 of 80 subjects (16%) in the CCP arm (relative risk, 0.52; 95% CI, 0.29 to 0.94; p=0.03). A modified intent-to-treat analysis excluding patients who experienced the primary end point prior to the study intervention found a relative risk of 0.4 (95% CI 0.20 to 0.81). While secondary end points (including life-threatening respiratory disease, oxygen supplementation at 100% FiO₂, noninvasive ventilation, ICU admission, mechanical ventilation, critical systemic illness, and acute respiratory failure) all trended towards benefit, differences were not statistically significant, with wide confidence intervals due to the small number of these events across both groups. A dose dependent effect was described, with a relative risk of 0.27 (95% CI 0.08-0.68) above a median titer of 1:3200 and a relative risk reduction of 0.69 (95% CI 0.34-1.31) below the median of 1:3200.

Observational Studies

Some observational and non-randomized studies published following the original EUA have shown potential benefit with early, high-titer CCP, or in specific subgroups, but findings have been variable, and minimal or no benefit has been seen in late disease once respiratory failure has progressed to the stage of requiring mechanical ventilation/intubation.

In an updated observational study using propensity score matching to non-transfused control patients, Salazar et al. observed improved mortality in subjects transfused within 72 hours of admission with high-titer CCP, but not in subjects transfused beyond 72 hours[11]. Additional analysis found an optimal window for transfusion within 44 hours of hospital admission for discriminating mortality within 60 days after transfusion.

An observational study comparing 263 patients hospitalized with severe COVID-19 treated under the EAP to 263 matched controls[12], found no statistical difference in 28-day mortality CCP cases (25.5%) compared to controls (27%, P = 0.06). 7-day mortality was statistically better for CCP cases (9.1%) than controls (19.8%, P < 0.001) and continued at 14 days (14.8% vs.23.6%, P = 0.01). Titers of the CCP transfused (1-2 units) were not available.

A non-randomized cohort study in Kuwait, in patients with moderate or severe COVID-19, found that CCP transfusion in 135 subjects was associated with a higher rate of clinical improvement compared to 233 matched controls receiving standard of care[13], but quantitative titers of the transfused CCP were not available.

A matched cohort analysis found no significant difference in survival in 64 patients who received CCP a median of 7 days after symptom onset compared to 177 matched controls[14].

An observational study of CCP transfused to 73 hospitalized COVID-19 patients within 72 hours of admission found no overall difference in mortality or oxygenation compared to propensity-score matched controls, although there was evidence of a mortality and oxygenation benefit in CCP recipients <65 years old[15]. In CCP recipients, pre-transfusion antibody titers were associated with mortality at day 28 in univariate analyses.

A recent observational case-control study found that hospitalized COVID-19 patients with severe respiratory failure who were transfused with CCP presented with already high titers of SARS-CoV-2 IgG antibodies before transfusion, and did not show improved survival at 30 days compared to matched controls[16].

Expanding on analyses made publicly available prior to the original EUA[17], a recent report from the national Expanded Access Protocol (EAP) sponsored by the Mayo Clinic described a survival benefit at 30 days following transfusion associated with early use of high titer CCP in hospitalized patients[18], where titer was measured by the Ortho VITROS IgG assay included as a CCP manufacturing test under this EUA. FDA has performed additional analyses of over 20,000 subjects enrolled in the EAP using multivariate Cox proportional-hazards regression that included titer (<250 versus >250 in a live virus neutralization assay), ventilation status, age, days from diagnosis to transfusion, gender, race, and hospital region as covariates. In findings similar to those at time of EUA issuance, there was a modest survival benefit associated with transfusion of high titer plasma (HR 0.93 [0.88,0.98] for high versus low titer) and with earlier transfusion (transfusion on same day of diagnosis: HR 1 [reference]; 1 to 3 days from diagnosis: HR 1.08 [0.93, 1.26]; 4 to 10 days from diagnosis: HR 1.23 [1.06, 1.43]; 11 days or more diagnosis: HR 1.23 [1.05, 1.44]). Patients aged 41-60 years (HR 1.53 [1.32, 1.78]), 61-80 years (HR 2.90 [2.50, 3.35]), and 81 years or older (HR 5.74 [4.92, 6.69]) were all more likely to experience death when compared to patients 40 years or younger, with an increasing hazard with each successive age category. Male sex was also associated with an increased hazard (HR 1.11 [1.05, 1.17]).

Finally, several reports of clinical improvement in immunosuppressed or immunodeficient patients treated with CCP, including after prolonged illness, support potential efficacy in this population and suggest a longer potential therapeutic window than in immunocompetent patients, but well-controlled data in these populations remain lacking[19-21].

Preclinical studies

Early preclinical studies using mouse and hamster models suggested potential benefit with passive immune therapies. More recently, macaque models found that passive transfer of immunoglobulins could provide protection against infection, as well as therapeutic efficacy following viral challenge, in a dose-dependent manner[22]. Higher doses were needed for therapeutic versus prophylactic efficacy. While the authors noted that their data demonstrated the therapeutic efficacy of convalescent plasma for treatment of infection, they cautioned that only high serum neutralizing antibody titers showed therapeutic benefit, potentially at levels that would be difficult to achieve via plasma transfusion.

Antibody responses in COVID-19 and timing of CCP transfusion

The relative roles of humoral and cellular immunity in SARS-CoV-2 infection continue to be unraveled, and it appears likely that CD4+ T cells, CD8+ T cells, and neutralizing antibody responses all contribute to control of SARS-CoV-2 infection in both non-hospitalized and hospitalized cases of COVID-19[23]. The large majority of patients with SARS-CoV-2 infection will seroconvert within 5-15 days post-symptom onset, with 90% seroconverting by day 10[23-25]. IgM and IgG antibodies are frequently detected concurrently[26], and peak anti-spike or anti-RBD IgG levels are reached by approximately 15 days post symptom onset[27]. Antibody responses and memory B cells appear to persist for at least 5 months and antibodies may be a correlate of immune protection[28-31]. Delayed antibody response kinetics also appear to be associated with more severe disease[27, 32]. At the same time, studies have generally shown higher titers in patients following recovery from severe disease compared to mild or asymptomatic illness[25, 33].

The observation that high titer CCP was beneficial when administered within 72 hours of symptom onset in high risk subjects, but failed to demonstrate benefit in trials where the median duration of symptoms was 8 days or longer, indicates benefit with CCP transfusion is more likely in patients early in the humoral immune response when host antibody titers remain undetectable or low (i.e., likely within the first week following symptom onset). This is consistent with longstanding historical precedent in passive immune therapies for viral infections, where prophylactic or early use has generally been more effective than in established infections[34].

These trends are also consistent with clinical evidence for administration of anti-SARS-CoV-2 monoclonal antibodies, where benefit has been demonstrated with early outpatient use, but not in hospitalized patients within 12 days of symptom onset[35-37] as described in the following two studies:

In outpatient studies of bamlanivimab in recently diagnosed patients with mild to moderate disease (BLAZE-1)[36], subjects were excluded if they were previously known to be seropositive. Subjects had a median of 4 days of symptoms at the time of infusion, and the study found one of three doses of neutralizing antibody LY-CoV555 appeared to accelerate the natural decline in viral load over time. While reduction in viral load was the primary endpoint in this phase 2 trial, subjects treated with bamlanivimab also showed a nominally statistically significant reduction in COVID-19 related hospitalizations or ED visits within 28 days in the pooled dose-level data.

In outpatient studies of casirivimab/imdevimab in symptomatic patients with mild to moderate COVID-19 (R10933-10987-COV-2067), subjects who were no more than 7 days from symptom enrollment were included regardless of serostatus[35]. Casirivimab/imdevimab treatment reduced viral load, and patients who were seronegative at baseline showed larger reductions in viral load and a larger reduction in the proportion of subjects with at least one medically attended visit compared to the overall population. Based on these studies, both therapies were granted EUA for use in high risk outpatients with mild to moderate COVID-19 (<https://www.fda.gov/media/143892/download>, <https://www.fda.gov/media/143603/download>).

In early studies of the COVID-19 pandemic, the median time from symptom onset to the development of dyspnea was approximately 5-8 days[38, 39], and patients who develop critical illness typically do so shortly thereafter (days 8-10)[40]. While the study by Libster et al[10] demonstrated a reduction in progression to severe disease in high risk outpatients within 72 hours of the onset of symptoms, one factor complicating very early use of CCP in the outpatient population is the evidence that a large proportion of these patients will have a self-limited illness and will not go on to severe or critical illness even without targeted intervention[41]. Therefore, in the early-disease outpatient population, it is important to have a full understanding of the relative benefit and identify high-risk populations so that the known and potential risks of transfusion are outweighed by the known and potential benefits of CCP. Ongoing randomized controlled trials will be critical to determine the clinical and laboratory parameters that can identify where the potential benefit of CCP outweighs the potential risk in outpatients.

Based on the study by Libster et al[10] the therapeutic window appears to be at least within 72 hours of symptom onset, while additional negative RCTs with a median duration of symptoms prior to transfusion of 8 days indicating that 8 days after symptom onset may be too late for efficacy of CCP in immunocompetent hospitalized COVID-19 patients. These timepoints appear to correlate with the timing of the patients' own antibody responses to infection, such that by the time a patient is forming their own antibodies, benefit from CCP appears unlikely. The time period between 3 and 7 days remains to be studied rigorously in randomized trials of CCP, but observational studies, preclinical studies, studies of related therapies, and what is known about the timing of the adaptive immune response in SARS-CoV-2 infection suggest that high titer CCP may be effective in this window period. As noted above, this window appears to be longer in the setting of impaired or deficient humoral immunity. Nonetheless, adequate and well-controlled trials in this time period remain necessary for a conclusive demonstration of efficacy.

Evaluation of EUA Criteria

Considering the emerging evidence summarized above, the EUA criteria based on FDA Guidance¹ were reevaluated to determine the ongoing eligibility of CCP for the treatment of hospitalized patients with COVID-19.

a. *Serious or life-threatening disease or condition*

COVID-19 is a serious or life-threatening disease or condition which has resulted in >380,000 deaths in the United States as of January 15, 2021, and large numbers of new infections and deaths continue to be reported (www.cdc.gov/coronavirus/2019-ncov/cases-updates/us-cases-deaths.html). Patients also have an increased risk of serious events such as thromboembolic events, cardiomyopathy and arrhythmia, renal injury, and stroke, which can result in long-term morbidity (<https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>). Therefore, COVID-19 continues to meet the criterion of a serious or life-threatening disease or condition.

b. *Evidence of Effectiveness*

Based on newly available evidence from randomized, controlled trials, observational studies, and preclinical studies summarized above, use of low titer CCP no longer meets the evidentiary standard of “may be effective”. Available evidence supports that high titer CCP is effective when administered within 3 days of symptom onset but is unlikely to be effective when administered 8 days or more following symptom onset in immunocompetent patients. The time period between 3 days and 7 days post symptom onset remains to be rigorously studied in randomized, controlled trials. However, in aggregate, the available data suggest a window for potential therapeutic efficacy if CCP is administered early (typically less than 7 days of symptom onset), with benefit most likely the earlier the CCP is transfused. Additional clinical and preclinical evidence on the role and timing of the humoral immune response COVID-19 summarized above are consistent with this being the period prior to a patient’s own antibody response.

In early reports from Wuhan, China, the median time from symptom onset to hospitalization was reported to be 7 days[38]. However, additional reports showed this time period shortened as the pandemic progressed and was as short as 1.5 days as awareness of SARS-CoV-2 increased[42]. Similarly, in an early US case series, the mean duration of symptoms at admission was 7±4 days[43], but a later report of 463 patients with COVID-19 in Detroit, MI, found 79-85% of patients had symptom duration of <7 days prior to admission[44]. Significant variability between countries and patient demographics has also been observed[45]. Considering the reported timing of hospitalization and time course of COVID-19, while highly variable, there appears to be a potential therapeutic window if CCP is administered to hospitalized patients early in the course of hospitalization. Recognizing the variability in patients’ courses of illness[46], underlying immune function, kinetics of antibody response, stage of disease at presentation to care, and CCP potency, a precise therapeutic window is difficult to define. Therefore, it is reasonable to consider that treatment of hospitalized COVID-19 patients continues to meet the standard of “may be effective”, although use early in the course of hospitalization should be emphasized over treatment of late, severe disease (e.g., in intubated and mechanically ventilated patients). In addition, use of high titer CCP in patients with impaired humoral immunity, including later in illness, appears to be associated with clinical improvement and meets the evidentiary standard of “may be effective” although the quality of evidence in these populations remains limited.

Several studies have failed to demonstrate benefit in intubated patients requiring mechanical ventilation, but these patients have generally been late in the time course of illness (>8-10 days). While expected to be rare, patients whose progression of disease requires intubation early in the course of illness, or who may have been intubated early for other pre-existing clinical reasons (e.g., acquired infection while already intubated, intubated for risk factors related to airway protection rather than ARDS), may still be in the early phase of the humoral immune response (i.e., prior to formation of neutralizing antibodies), and could potentially benefit from passive immune therapy, including CCP transfusion. Also, as noted above, patients with impaired humoral immunity may have a longer therapeutic window for efficacy, including following intubation and mechanical ventilation. Therefore, an exclusion based solely on intubation status does not appear justified at this time, especially considering the acceptable safety profile of CCP demonstrated to date.

Ongoing trials in diverse clinical settings, including multicenter outpatient and inpatient clinical studies, will be critical to the continued evaluation of safety and efficacy of CCP for the treatment of COVID-19. Patients should continue to be encouraged to enroll in randomized, controlled trials when available.

c. ***Risk-Benefit Analysis***

Potential benefits of CCP as outlined above and in the prior EUA include reduced progression to severe disease, improved mortality with early treatment, and improved viral clearance.

Risks are expected to include those inherent to plasma transfusion[47]:

- Transfusion related acute lung injury (TRALI)
- Transfusion associated cardiac overload (TACO)
- Allergic/Anaphylactic reactions
- Febrile nonhemolytic transfusion reactions
- Transfusion-transmitted infections
- Hemolytic reactions

The risks of these events observed in trials to date appear to be within the expected rates of these events for transfusion of plasma in critically ill patients[48-50].

Additional risks specific to convalescent plasma include a theoretical risk of antibody-dependent enhancement (ADE) and a theoretical risk of suppressed long-term immunity. Antibody-dependent enhancement of disease is thought to occur when antibodies to an infectious agent ‘bridge’ the pathogen to Fc receptors on immune cells leading to increased viral entry and enhancement of infection[51]. No evidence of antibody-dependent enhancement of disease has been observed in the studies of CCP summarized above, and the potential for ADE with the use of CCP remains theoretical at this time.

The potential of passive immune therapies to suppress long-term immunity in recovered or vaccinated patients has not been evaluated in clinical studies to date. Current CDC guidance recommends that patients who receive CCP for the treatment of COVID-19 defer vaccination for at least 90 days as a precautionary measure until additional information becomes available, to avoid potential interference of the antibody therapy with vaccine-induced immune responses (<https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html>). Ongoing trials will evaluate antibody responses to infection following treatment with CCP.

Summary of Risk-Benefit Analysis

The available evidence indicates a lack of benefit with the use of low titer CCP in the treatment of COVID-19. Therefore, considering the known risks of plasma transfusion outlined above, the

known and potential benefits of low titer CCP use no longer outweigh the known and potential risks.

Additional RCTs to date have demonstrated benefit with transfusion of high titer CCP within 3 days of symptom onset, and a lack of benefit in hospitalized COVID-19 patients in studies at a median of 8 days or later post symptom onset. These findings suggest CCP is less likely to be effective when the host humoral response has already been established. While the study by Libster et al demonstrated benefit in the outpatient setting, the known and potential benefits in the outpatient setting when disease is still mild must be weighed against known and potential risks of plasma transfusion. Because many patients very early in disease (within 72 hours of symptoms) will have mild to moderate self-limited disease, and adverse events associated with plasma transfusion can be serious or even fatal, additional data from randomized controlled trials in the outpatient setting are needed to assure that known and potential risks are outweighed by known and potential benefits in outpatients. Such studies are underway and will continue to inform this risk-benefit analysis.

As noted above, based on results from RCTs and the EAP, the safety profile of CCP appears comparable to that of plasma transfusion in general. Considering this safety profile, it is reasonable to believe that the known and potential benefits of high titer CCP outweigh the known and potential risks when used for the early treatment of hospitalized COVID-19 patients. Based on what is known about the typical course of illness and kinetics of the humoral immune response in COVID-19, for most patients, early treatment likely represents within one week of symptom onset. However, considering the large variability in the course of illness in COVID-19, and the variability in host immune function and kinetics, a specific timeframe for efficacy cannot be defined based on available data to date. Furthermore, the therapeutic window may be longer when CCP is administered to patients with clinical or laboratory evidence of impaired humoral immunity.

d. *No alternatives*

While several therapeutics have been granted emergency use authorization, only Remdesivir has been approved for the treatment of COVID-19. However, for the purposes of determining the eligibility of CCP for EUA under section 564 of the Federal Food, Drug, and Cosmetic Act (21 USC 360bbb-3), Remdesivir is not considered an adequate alternative for the treatment of hospitalized patients with COVID-19. Therefore, CCP continues to meet this criterion because there are currently no adequate, approved, and available alternatives to CCP for the treatment of hospitalized patients with COVID-19.

In sum, the EUA for CCP should be revised so that the eligibility criteria for Emergency Use Authorization outlined in FDA guidance¹ continue to be met. The conditions of Emergency Use Authorization for CCP in hospitalized patients with COVID-19 should be revised to exclude the use of low titer CCP. High titer CCP continues to meet criteria for Emergency Use Authorization for the treatment of hospitalized patients with COVID-19 early in the course of hospitalization, and the letter of authorization and accompanying fact sheets should be revised to emphasize early transfusion in the absence of immunodeficiency or immunosuppression. Additional results from adequate and well-controlled trials will continue to be evaluated to further characterize the patient populations and product

characteristics meeting EUA criteria and patients should be encouraged to enroll in these trials when available.

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