U.S. FOOD & DRUG ADMINISTRATION

CLINICAL MEMORANDUM

From:	(b) (6), OBRR/DBCD/CRS
To:	(b) (6), OBRR
Through:	(b) (6), OBRR/DBCD (b) (6), OBRR/DBCD (b) (6), OBRR/DBCD/CRS
Re:	EUA 26382: Emergency Use Authorization (EUA) Request (original request 8/12/20; amended request 8/23/20)
Product:	COVID-19 Convalescent Plasma
Items reviewed:	EUA request Fact Sheet for Health Care Providers Fact Sheet for Recipients
Sponsor:	Robert Kadlec, M.D. 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), an unapproved biological product, is proposed for use under an Emergency Use Authorization (EUA) under section 564 of the Federal Food, Drug, and Cosmetic Act (the Act),(21 USC 360bbb-3) as a passive immune therapy for the treatment of hospitalized patients with COVID-19, a serious or life-threatening disease. There currently is no adequate, approved, and available alternative to CCP for treating COVID-19. The sponsor has pointed to four lines of evidence to support that CCP may be effective in the treatment of hospitalized patients with COVID-19: 1) History of convalescent plasma for respiratory coronaviruses; 2) Evidence of preclinical safety and efficacy in animal models; 3) Published studies of the safety and efficacy of CCP; and 4) Data on safety and efficacy from the National Expanded Access Treatment Protocol (EAP) sponsored by the Mayo Clinic.

Considering the totality of the scientific evidence presented in the EUA, I conclude that current data for the use of CCP in adult hospitalized patients with COVID-19 supports the conclusion that CCP meets the "may be effective" criterion for issuance of an EUA from section 564(c)(2)(A) of the Act. It is reasonable to conclude that the known and potential benefits of CCP outweigh the known and potential risks of CCP for the proposed EUA. Current data suggest the largest clinical benefit is associated with high-titer units of CCP administered early in the

course of disease. Adequate and well-controlled randomized trials remain necessary for a definitive demonstration of CCP efficacy and to determine the optimal product attributes and appropriate patient populations for its use.

Recommendation: CCP meets the eligibility criteria for EUA under section 564 of the Act.

Introduction and Background

SARS-CoV-2 and COVID-19

The novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), identified in December 2019, causes a respiratory illness known as COVID-19. Clinical manifestations of COVID-19 range from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multiorgan failure, and death[1, 2]. The World Health Organization declared COVID-19 a global pandemic on March 11, 2020 and the virus has caused more than 5,000,000 cases and more than 170,000 deaths in the United States as of August 20, 2020.

Frequently reported symptoms in COVID-19 include fever, cough, shortness of breath, myalgia or fatigue, loss of taste or smell, headache, and gastrointestinal symptoms (https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html). Severe disease can result in acute respiratory distress syndrome (ARDS), sepsis and septic shock, cardiomyopathy and arrhythmia, acute kidney injury, and thromboembolic events. Early reports from the outbreak[3] demonstrated that 81% of cases resulted in mild disease (non-pneumonia, or mild pneumonia). 14% of cases resulted in severe disease (dyspnea, RR>30, SpO2<93, PaO2/FiO2<300, lung infiltrates) and 5% resulted in critical illness. Risk factors for severe illness include older age, type II diabetes mellitus, cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, immunocompromised state from solid organ transplant, sickle cell disease, and serious heart conditions such as heart failure or cardiomyopathy (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-increased-risk.html).

FDA has not yet approved any therapeutics for the treatment of COVID-19. Studies demonstrated improved mortality with use of dexamethasone in hospitalized patients requiring oxygen support of mechanical ventilation[4]. The antiviral agent remdesivir shortened time to recovery in adults hospitalized with COVID-19[5] and was granted emergency use authorization on May 1, 2020. Additional treatment consists largely of supportive care. A variety of therapeutics have been proposed or are currently under clinical investigation including immunomodulatory agents and other antiviral agents (https://www.covid19treatmentguidelines.nih.gov/).

Passive antibody therapy and convalescent plasma

Among the experimental treatment modalities discussed by the scientific community are the use of immune convalescent plasma or serum, and similarly, hyperimmune globulin from recovered COVID-19 patients[6]. This treatment entails the administration (or transfusion) of plasma (or derivatives thereof) from individuals following resolution of infection under the rationale that

antibodies in the plasma that are transferred to recipients (frequently described as passive antibody therapy) are able to neutralize the virus and protect recipients from infection or prevent or mitigate progression of existing infection. While hyperimmune globulin products might be expected to provide such antibodies in a better-characterized and more consistently manufactured product, convalescent plasma is more rapidly available, has been widely used under the EAP (>70,000 transfused at the time of this writing), and is under investigation in several randomized controlled trials in diverse clinical scenarios (e.g. severe disease, early disease, prophylaxis), localities, and with varying controls (e.g., non-immune plasma, colloid, standard of care).

Passive antibody therapy, including convalescent plasma, has been proposed or used to treat a wide variety of infectious diseases for more than a century, including several respiratory viral illnesses such as influenza, Respiratory Syncytial Virus (RSV), Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS)[7-9]. Examples of hyperimmune globulin used to treat post-exposure prophylaxis include Hepatitis B and Rabies. Passive immune therapy has been used to treat patients who are already manifesting symptoms of varying severity, but it is thought to be most effective when administered prophylactically (e.g., prior to clinical or laboratory evidence of infection); when used for treatment of symptomatic disease, immune plasma is thought to be most effective when administered early after the onset of symptoms. However, well-controlled studies in this field are rare.

Declaration of Public Health Emergency

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, 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. Pursuant to section 564 of the Act, and on the basis of such determination, the Secretary of HHS then 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 terms of any authorization issued under that section.

Product Description

CCP is human plasma collected by FDA registered blood establishments 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 are qualified.

The manufacture of CCP includes testing for anti SARS-CoV-2 antibodies as a manufacturing step to determine titer levels before release. Units tested by the Ortho VITROS SARS-CoV-2 IgG test as part of manufacture and found to have a signal-to-cutoff (S/C) ratio of 12 or greater qualify as High Titer COVID-19 Convalescent Plasma. If a center is considering using an alternative test in manufacturing in order to qualify High Titer CCP, they should contact CBER to determine acceptability of the proposed test, which if accepted, would require an amendment to the EUA.

Units containing anti-SARS-CoV-2 antibodies but not qualified as High Titer COVID-19 Convalescent Plasma by the test described above are considered low titer units and must be

labeled as "COVID-19 Convalescent Plasma of Low Titer". These units are authorized for use. Health care providers can decide whether to use the units based on an individualized assessment of benefit:risk. FDA will continue to evaluate this authorized use based on additional data that become available.

Proposed Indication

Under this EUA request, the Assistant Secretary for Preparedness and Response (ASPR) is proposing the use of COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19.

Proposed Dosing

Health care providers will administer CCP according to standard hospital procedures and institutional medical and nursing practices.

Clinical dosing may first consider starting with one CCP unit (about 200 mL), with administration of additional CCP units based on the prescribing physician's medical judgement and patient's clinical response.

Patients with impaired cardiac function and heart failure may require a smaller volume or more prolonged transfusion times.

Prior Human Experience

Early data on the use of convalescent plasma came in the form of two case series from the initial outbreak in China[10-12]. These studies in patients with very severe illness found that patients showed improved viral load, symptoms, and radiographic findings. The case series suggested CCP may be helpful but were limited by their small size and lack of controls.

Following these initial reports, a large number of clinical trials have been initiated, but most have not yet reported results. Available data generally fall into one of four categories: randomized controlled trials, controlled trials based on availability of plasma but not truly randomized, retrospective matched cohorts (e.g., propensity score matched), and case series/single-arm studies[1]. The detailed findings of these studies are described under "Evidence of Effectiveness" below. In brief, the studies include:

Randomized controlled trials

The two randomized controlled trials reported to date[13, 14] were conducted in Wuhan, China[13], and the Netherlands[14].

Controlled trials

In addition to the randomized controlled trials, prospective trials in which the control patients were those who were not transfused due to plasma unavailability, have also been reported[15-

[1] Several reports remain in pre-print status and have not been peer-reviewed at the time of this review

17]. Some of these studies provide encouraging signs of effectiveness, with limitations based on the not-truly-randomized nature of the study designs.

Retrospective matched cohort studies

Several reports of retrospective matched cohort studies of CCP have been made publicly available. [18-21]. These studies generally found a trend towards improved mortality when patients were treated earlier in the course of disease. One study found an association between antibody titer and clinical response[21]. These studies used varying approaches to matching, and based on the retrospective nature of their designs, may be subject to bias and confounding.

Case Series

Several investigators have reported case series and single arm studies ranging in size from 5 to 31 patients and across several countries, including the reports from the early pandemic in China described above [10, 11, 22-26].

Expanded Access

The EAP sponsored by the Mayo Clinic was established in April 2020 and has enrolled >90,000 subjects as of August 13, 2020. The goal of this uncontrolled, single-arm study is to provide access to CCP 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. Initial reports from this study by Joyner et al described safety findings and outcomes in the first 5,000[23], and then 20,000 subjects[24]. Additional findings from this study are detailed in the next section of this memorandum.

Eligibility for an EUA

FDA may only issue an EUA if several statutory criteria, outlined in section 564(c) of the Act, are met. These criteria are further explained in an FDA guidance document, (https://www.fda.gov/media/97321/download), and with respect to CCP, are listed below in italics followed by this reviewer's assessment:

a. Serious or life-threatening disease or condition

Severe COVID-19 requiring hospitalization is a serious or life-threatening disease or condition that has resulted in >170,000 deaths in the United States as of August 20, 2020 (www.cdc.gov/coronavirus/2019-ncov/cases-updates/us-cases-deaths.html). Patients 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).

b. Evidence of Effectiveness

The sponsor has pointed to four lines of evidence in support of the use of COVID-19 convalescent plasma in the treatment of hospitalized patients with COVID-19:

1. History of convalescent plasma for respiratory coronaviruses

A systematic review of passive antibody therapy for SARS coronavirus (SARS-CoV-1) and severe influenza found a trend towards reduction in mortality, but noted that studies were commonly of low or very low quality, lacked control groups, and were at risk of bias[27].

An uncontrolled study involved the treatment of 80 patients in Hong Kong with SARS-CoV-1 infection[28]. A higher day-22 discharge rate was observed among patients who were given convalescent plasma before day 14 of illness (58.3% vs 15.6%; P<0.001) and among those who were PCR positive and seronegative for coronavirus at the time of plasma infusion (66.7% vs 20%; P=0.001). A small retrospective nonrandomized study of patients with progressive SARS-CoV-1 infection after ribavirin and pulse methylprednisolone treatment showed that the plasma-treated group had a shorter hospital stay and lower mortality than the group that continued treatment with pulse methylprednisolone[29]. These reports followed a single case report of successful convalescent plasma therapy in a 57-year-old woman with SARS-CoV-1 infection in Hong Kong[30]. In addition, a case series of three patients with SARS-CoV-1 infection in Taiwan were treated with convalescent plasma, resulting in a reduction in viral load; all three recipients survived[31].

Treatment with convalescent plasma was also reported in three patients in South Korea with MERS, but researchers found only a subset of convalescent plasma showed neutralizing activity[32]. A group in Saudi Arabia reported on the feasibility of collecting convalescent plasma for passive immunotherapy of Middle East respiratory syndrome coronavirus (MERS-CoV) infection by using ELISA to screen serum samples from 443 potential plasma donors[33]. They found only a small subset (9 patients) showed neutralization activity and concluded trials would be challenging because of the small pool of donors with sufficiently high titers.

2. Evidence of preclinical safety and efficacy in animal models

In mouse models of SARS-CoV-1 infection, passive transfer of immune serum to naïve mice prevented virus replication in the lower respiratory tract following intranasal challenge[34].

Animal models of SARS-CoV-2 infection have been established in hamsters susceptible to SARS-CoV-2 infection and in mice transduced with hACE2 to sensitize them to the SARS-CoV-2 infection. Hamster studies found that postinfection sera from hamsters previously infected with the virus administered to other hamsters following infection with SARS-CoV-2 was able to decrease viral loads[35]. A separate study found immunoprophylaxis with early convalescent serum achieved a significant decrease in lung viral load but not in lung pathology[36]. In mouse studies, administration of 150 μL of human CCP one day prior to SARS-CoV-2 infection prevented weight loss and lung tissue histological changes, and accelerated the rate of virus clearance[37]. More rapid clearance of SARS-CoV-2 infection was not observed after treatment with pooled plasma from SARS-CoV-1 survivors or MERS survivors.

3. Published studies of the safety and efficacy of COVID-19 convalescent plasma

Randomized controlled trials – Results from two RCTs results have been made publicly available.

The first study by Li et al. in Wuhan, China[13], was in patients with severe to life-threatening COVID-19 who were transfused with 4-13 mL/kg of CCP with an ELISA titer >1:640. The primary outcome was time to clinical improvement within 28 days from randomization, and the study found clinical improvement in 27/52 (51.9%) in the CCP arm, and 22/51 (43.1%) in the control arm (p=0.26). When examining subgroups by disease severity they found that, in severe disease, 21/23 (91.3%) in the CCP arm and 15/22 (68.2%) in the control arm [p=0.03] showed clinical improvement. In life-threatening disease, 6/29 (20.7%) in CCP and 7/29 (24.1%) in control (p=0.83) showed clinical improvement. However, there was a non-significant test for interaction (p=0.17), so the results in the subgroups should not be interpreted differently. CCP treatment was associated with higher rates of negative SARS-CoV-2 viral PCR results from nasopharyngeal swabs at 24, 48, and 72 hours. Of note, the median duration of symptoms at the time of transfusion was 30 days. The study was stopped early due to low enrollment as a result of improved case rates in the Wuhan region, and thus may have been underpowered to detect statistically significant clinical benefit.

The second RCT by Gharbharan et al. in the Netherlands[14] examined patients with clinical COVID-19 as determined by a positive test in the previous 96 hours before enrollment (most patients met criteria for severe disease with a median of 10 days of symptoms at transfusion) who were treated with 300 mL of CCP with a neutralization titer of at least 1:80. The primary outcome was overall mortality until discharge. The trial was stopped early because they observed that antibody titers in the recipients were already high at the time of transfusion, and therefore, they made a decision to halt and redesign the trial because the presumed benefit would be in patients earlier in disease. At the time of study stopping, 6 of 43 CCP patients (14%) had died and 11 of 43 control patients (26%) had died. The prespecified comparison of adjusted mortality showed no difference (OR 0.95 [0.2-4.67]), but the study may have been underpowered to detect statistically significant clinical benefit at study stopping.

Controlled trials (non-randomized) – Two studies from the Middle East[15, 16] reported prospective trials in which the control patients were those who were not transfused due to a lack of plasma availability[16] or “As a result of ABO compatibility and limited plasma…randomly chosen to take CP”[15]. A third study where controls were also based on plasma availability was reported out of China[17].

A study by Rasheed et al[15] examined CCP transfusion in patients admitted to the ICU for less than 3 days (mean of 14-16 days of symptoms) and found that 1 of 21 CCP patients (4.8%) and 8 of 28 (28.6%) control patients died within the observation period, with only one patient experiencing a mild allergic reaction. This study is limited by the lack of formal reporting of statistical approaches.

A study by Abolghasemi et al[16] likewise compared CCP transfused patients to controls who were not transfused due to plasma unavailability within 3 days of enrollment. Patients had severe disease and were enrolled if they were within 7 days of illness onset. Patients were transfused

with 500-1000 mL of CCP confirmed to have anti-SARS-CoV-2 antibodies by a semi-quantitative ELISA. The primary outcomes were described as survival and hospital length of stay. All-cause mortality was 17/115 (14.8%) in the CCP arm versus 18/74 (24.3%) in the control arm [p=0.09]. The mean hospital length of stay was 9.5 days in CCP arm versus 12.9 in the control [p=0.002]. 107 (93%) CCP patients were discharged versus 59 (79.7%) in the control [p=0.006].

A third study where controls were also based on plasma availability was reported out of China[17]. Patients treated with CCP showed significantly improved viral clearance (6/6 CCP (100%), 4/15 controls (26.7%), p=0.004). However, no significant differences in mortality were seen (5/6 (83%) died in CCP arm, 14/15 (93%) died in control arm, p=0.5), noting there was high mortality in this very small, critically ill cohort.

Retrospective matched cohort studies – Several reports of retrospective matched cohort studies of CCP have been made publicly available [18-21].

In severe to life-threatening COVID-19, Liu et al[19] found that CCP transfusion was significantly associated with improved survival in non-intubated patients (hazard ratios: 0.19 (95% CI: 0.05 ~0.72); p=0.015), but not in intubated patients. CCP recipients were more likely than controls to remain the same or have improvements in supplemental oxygen requirements at day 14 (OR 0.86, p =0.028).

Using a propensity score matching algorithm, Salazar et al[21] found 28-day mortality was 3.7% in 136 CCP transfused subjects with severe COVID-19 versus 7.6% in 543 non-transfused controls (p=0.13). In those transfused within 72 hours of admission and with high-titer units, there was a significant difference in 28-day mortality (1.2% in CCP vs 7.0% in control, p = 0.047). The authors concluded that transfusion of high anti-RBD IgG titer COVID-19 CCP early in hospitalization reduces mortality.

In smaller studies, Perotti et al and Hegerova et al found similar trends toward benefit but noted that trends would need confirmation in well-controlled randomized trials[18, 20].

These studies are subject to several limitations due to their retrospective nature. For example, the number of variables used for subject-control matching may be insufficient to assure comparability of the treated patients and the untreated controls. If subjects and controls are selected from the same health care facility and they are well matched, it would be unclear whether there were other confounding factors that led to one patient receiving the plasma and the other seemingly comparable patient not receiving the plasma. If the decision to transfuse was based on a clinical condition that is associated with the outcome of interest (survival), but that is not captured in the matching, this can make treated and untreated patients incomparable and bias the studies. Finally, all are subject to a potential period effect because mortality has been observed to decrease generally over the course of the pandemic, for reasons that remain unclear.

Case series - Several investigators have reported case series and single arm studies ranging in size from 5 to 31 patients and across several countries, including the reports from the early pandemic in China described above [10, 11, 22-26]. Some case reports have highlighted patient improvement in patients with impaired humoral immunity such as X-linked agammaglobulinemia[38] and following lymphocyte depleting chemotherapy[39], although the

relative role of B cells in COVID-19 disease remains uncertain[40]. While the remaining case series and reports are encouraging with respect to the improvement seen in these patients, the interpretation of the results of case series are limited by the absence of controls [12, 22, 25, 26, 41].

4. Data on safety and efficacy from the EAP sponsored by the Mayo Clinic.

In section 6.4 “Clinical Safety and Efficacy” of the CCP EUA request, the sponsor has summarized a safety and efficacy analysis of data obtained from the EAP. This reviewer notes that the primary objective of the Mayo Clinic EAP was to provide access to convalescent plasma, with a secondary objective of demonstrating safety of CCP. Efficacy analyses were described in the protocol as exploratory analyses, and no pre-specified analysis plan was included in the protocol. Accordingly, this single-arm open-label protocol was broadly inclusive, and data collection was limited to encourage rapid roll out of the program, minimize administrative barriers to participation of study investigators, and achieve the primary objective of the program.

Safety: A report of adverse events in the initial population of 20,000 subjects in the EAP[24] found low overall rates of serious adverse events (SAEs). These included transfusion reactions (n=89; <l%), thromboembolic or thrombotic events (n=87; <l %), and cardiac events (n=680, 3%). Notably, the vast majority of the thromboembolic or thrombotic events (n=55) and cardiac events (n=562) were judged to be unrelated to the convalescent plasma transfusion. The seven-day mortality rate was 8.6% (8.2%, 9.0%), and was higher among more critically-ill patients relative to less ill counterparts, including patients admitted to the intensive care unit vs. not admitted (10.5% vs. 6.0%), mechanically ventilated vs. not ventilated (12.1% vs. 6.2%), and with septic shock or multiple organ dysfunction/failure vs. those without dysfunction/failure (14.0% vs. 7.6%).

In addition to the published safety information, additional safety reports and a Data Safety Monitoring Board report for the EAP have been submitted to FDA under the IND file for the EAP. In these reports, SAEs and suspected unexpected serious adverse reactions (SUSARs) did not occur at a rate that raised a safety concern beyond the risks known to be associated with plasma transfusion in patients with critical illness (e.g., severe COVID-19)[42-45]. The lack of a control population limits interpretation of the safety data and many of these adverse events may be difficult to evaluate in the context of severe COVID-19.

Efficacy: The sponsor has provided results from an analysis comparing clinical outcomes in subjects enrolled in the EAP who were treated with different levels of neutralizing antibodies, as assessed with three different assays. This analysis was performed in collaboration with the Mayo Clinic and the FDA Center for Biologics Evaluation and Research (CBER), and this reviewer notes that the analysis was provided, in part, by FDA investigators. While a statistical plan was specified prior to analysis of antibody titers with respect to outcomes as part of the FDA analysis, no analysis plan was specified in the original EAP protocol. Because measurement of the neutralizing antibody titer of the CCP was not required under the EAP, it was expected that patients would receive a wide range of neutralizing antibody titers. As neutralizing activity of antibodies in CCP is thought to be the primary mechanism of action for potential efficacy,

demonstration of a dose-response relationship between neutralizing antibody titers and clinical outcomes would provide early evidence of the efficacy of CCP.

At the time of this review, there were no validated assays for quantification of neutralizing anti-SARS-CoV-2 antibodies for measuring titer levels in plasma for the purpose of determining whether units measured meet the standards identified in the EUA for the manufacture of CCP. The assays described in the EUA submission include: a neutralization assay performed by the Broad Institute using native SARS-CoV-2 virus with detection of infected cells by (b) (4) (b) (4) a semiquantitative assay of IgG against spike protein (Ortho VITROS IgG); and a neutralization assay using a pseudo-typed (b) (4) bearing SARS-CoV-2 spike protein (Mayo Clinic). Among these assays, it appears the testing performed by the Broad Institute is the closest to the gold-standard of a plaque reduction neutralization titer in that this assay uses the native SARS-CoV-2 virus to determine the titer required for 50% inhibition of infection of cultured cells (ID50). FDA/CBER separately received data from a set of CCP samples comparing the correlation between these assays. While these assays generally correlated with each other, precise performance characteristics based on a reference panel or gold-standard methodology (plaque reduction neutralization titer) were not available at the time of this review.

In these assays, an ID50 titer cutoff of 250 in the Broad Institute assay was chosen to distinguish between high titer and low titer plasma. This value correlated with an Ortho VITROS IgG assay signal to cutoff (S/C) of 12. Based on titer data using the Broad Institute assay, the data submitted in the EUA demonstrate the following findings:

- There was no difference in 7-day survival in the overall population between subjects transfused with high versus low titer CCP.
- In the subset of non-intubated patients, there was a 21% reduction in 7-day mortality (from 14% to 11%, p=0.03) in subjects transfused with high versus low titer CCP.
- There was no apparent association between neutralizing antibody titers and 7-day mortality in intubated subjects.
- In additional analyses of a post-hoc subgroup of patients less than 80 years of age who were not intubated and who were within 72 hours of diagnosis, a stronger relationship between neutralizing antibody titers and 7-day mortality is observed. When titers are binned to low versus high at a threshold of 250, the sponsor reports a significant reduction in 7-day mortality from 11.3 to 6.3% (p = 0.0008).
- In additional analyses of survival using a Kaplan-Meier approach, the survival trends observed at 7 days persisted over a longer time period, with significantly improved survival in non-intubated patients (Figure 2, p=0.032) and a larger benefit in the subset of patients not intubated at the time of treatment, less than 80 years of age, who were treated within 72 hours of diagnosis (Figure 3, p=0.0081)

In additional analyses performed by FDA of the relationship between antibody titers and outcomes in the EAP data, similar trends were seen across the Broad Institute neutralization assay, a semiquantitative assay of IgG against spike protein (Ortho VITROS IgG), and a neutralization assay using a pseudo-typed (b) (4) bearing SARS-CoV-2 spike protein (Mayo Clinic).

Additional analyses of data from the EAP were posted publicly by Mayo Clinic investigators and collaborators[46]. In their analyses, the investigators observed an association between reductions in adjusted 7-day and 30-day mortality and earlier transfusion (<=3 days) of CCP and high antibody levels. Antibodies were measured using the Ortho VITROS IgG semiquantitative assay. Low, medium, and high antibody levels were defined as <4.62, 4.62-18.45, and >18.45 (S/C ratio), respectively.

Summary of Evidence of Effectiveness

Considering the totality of the scientific evidence summarized above, I agree that current data support the conclusion that CCP to treat hospitalized patients with COVID-19 meets the "may be effective" criteria for issuance of an EUA. Adequate and well-controlled randomized trials remain nonetheless necessary for a definitive demonstration of CCP efficacy and to determine the optimal product attributes and the appropriate patient populations for its use.

Current evidence suggests that benefit is most likely in patients treated early in the course of the disease (e.g., prior to intubation). In addition, as outlined in the data reviewed above from different studies, there is a potential benefit of CCP in intubated and non-intubated patients. Considering the absence of a control population in the EAP and that data from randomized trials remain limited, the lack of benefit observed in intubated patients in this study is currently insufficient to exclude potential benefit in this population. Therefore, bearing in mind the safety profile observed to date, inclusion of intubated and non-intubated patients under the EUA appears appropriate at this time.

Current evidence suggests that units with higher antibody content or neutralization activity are more likely to be effective. The identification of effective antibody levels or neutralizing activity levels is limited by the unavailability of validated assays for this purpose as part of the manufacture of CCP. However, if one considers the use of quantitative antibody or neutralization activity tests as a manufacturing test of product potency, the available data support use of the Ortho VITROS IgG assay for this purpose. The sponsor's recommended S/C cutoff of 12 or greater correlates with a neutralizing antibody titer of 250 in the Broad Institute's neutralizing antibody assay and accordingly, is acceptable as cutoff to qualify High Titer CCP. Other assays that have been validated to correlate with comparable anti SARS-CoV-2 antibody titers and provide similar quantitative assessment of neutralization activity may be acceptable for this purpose. If a blood establishment is considering using an alternative test in manufacturing in order to qualify High Titer CCP, they should contact CBER to determine acceptability of the proposed test, which if accepted, would require an amendment to the EUA.

Although higher titer units appear to be associated with improved survival in the EAP, this reviewer notes that the efficacy analysis of the EAP did not include an untreated (or placebo) control population. The EAP study showed a gradient of mortality in relation to the antibody level in the transfused CCP. This finding of a dose-response between antibody level and reduction in mortality provides evidence that the antibody is the active agent in convalescent plasma for treatment of COVID-19. This is consistent with the long history and biological basis of the use of convalescent plasma in treating infectious diseases.

The minimal antibody titer that would be effective in different patients has not been defined. It is expected to vary based on a number of factors, such as the potency of the antibody (itself dependent on the CCP donor), the volume transfused, the severity of the illness, the duration of the illness, and the time of administration of CCP relative to the patient diagnosis. Furthermore, a trend towards improved outcomes was observed at lower titer thresholds than those proposed in the EUA in some of the analyses of the EAP performed by the Mayo Clinic[46].

Therefore, based on findings which suggest that the antibody is the active agent in convalescent plasma, past experience, and the number of studies described earlier in this memo showing evidence of effectiveness of CCP, CCP not qualified as High-Titer by the Ortho VITROS assay still meets the evidentiary standard of "may be effective". These units will be labeled as "COVID-19 Convalescent Plasma of Low Titer". Health care providers will decide whether to use the units based on an individualized determination of potential benefit and risk.

c. Risk-Benefit Analysis

Potential benefits include potential improved survival and viral clearance in hospitalized patients with COVID-19. These potential benefits are based on the summary of effectiveness outlined above.

Risks are expected to include those inherent to plasma transfusion:

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

Some plasma transfusion risks, such as TRALI and TACO, would be expected to be elevated in patients with baseline pulmonary injury or impaired cardiac function, respectively. However, the actual risks of these events observed in the EAP population[24] were within the expected rates of these events for transfusion of plasma in critically ill patients[43, 45].

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[47]. The potential for ADE was explored in macaque models of SARS-CoV-1[48] wherein investigators found that passively transferred antibodies could skew inflammatory responses, potentially leading to exacerbation of pulmonary pathology. However, no overt evidence of ADE has been observed in the studies of CCP summarized above. As a result of the lack of adequately powered randomized controlled studies, this theoretical risk cannot be excluded at this time.

The potential of passive immune therapies to suppress long-term immunity in recovered patients has not been evaluated in clinical studies to date. Ongoing trials will evaluate antibody responses following treatment with CCP.

CCP may be contraindicated in patients with a history of severe allergic reactions or anaphylaxis to plasma transfusion.

Summary of Risk-Benefit Analysis

Based on the above, it is reasonable to believe that the known and potential benefits of CCP outweigh the known and potential risks of CCP for the proposed EUA. 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, will continue to inform this risk benefit assessment.

d. No alternatives

There are currently no adequate, approved, and available alternatives to CCP for the treatment of COVID-19. Remdesivir has been granted emergency use authorization but is not an approved treatment at the time of this writing.

In sum, the proposed EUA for CCP meets the eligibility criteria for Emergency Use Authorization under section 564 of the Act.

Fact Sheets for Healthcare Providers and Recipients

The Fact Sheet for Health Care Providers and Fact Sheet for Recipients were reviewed, and suggested revisions sent to the sponsor. The revised Fact Sheets are accurate, not misleading, and appropriate for the intended setting.

Conclusions

- COVID-19 Convalescent Plasma meets the eligibility criteria for Emergency Use Authorization.
- COVID-19 Convalescent Plasma may be effective in the treatment of COVID-19 and it is reasonable to believe that the known and potential benefits of CCP outweigh the known and potential risks of the product for the proposed EUA.
- Current evidence suggests clinical benefit is most likely in patients treated early in the course of the disease (e.g., prior to intubation) and with the use of CCP with higher antibody levels or neutralization activity.
- Current data are limited by the unavailability of validated assays of antibody levels or neutralization activity in CCP. Based on the available data, it is reasonable to use the Ortho VITROS IgG assay with an S/C cutoff of 12 or greater as a manufacturing potency test to qualify high titer units of CCP.

- Based on the available evidence, CCP without a result of 12 or greater in the Ortho VITROS assay meets the criteria for issuance of an EUA because, among other things, it is reasonable to believe it may be effective in treating COVID-19 and the known and potential benefits of the product outweigh its known and potential risks. Such units must be labeled as "COVID-19 Convalescent Plasma of Low Titer." Health care providers can decide whether to use these units based on an individualized determination of potential benefit and risk.
- The Fact Sheet for Health Care Providers and Fact Sheet for Recipients are accurate, not misleading, and appropriate for the intended setting.
- Randomized controlled trials are required to show definitive evidence of safety and efficacy and to determine the optimal product attributes and appropriate patient populations for the use of COVID-19 Convalescent Plasma.

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