DEPARTMENT OF HEALTH & HUMAN SERVICES

FOOD AND DRUG
ADMINISTRATION
Silver Spring, MD 20993

CLINICAL REVIEW MEMO

Re:	**BLA 101766/5169**
Product	COVID-19 Convalescent Plasma
Sponsor	OneBlood
Reviewed	Carlos Villa MD, PhD, Associate Director for Special Programs
Date Reviewed	11/15/2024
To	File
Through	Wendy Paul MD Deputy Director Division of Blood Components and Devices
ADD	6/10/2025

Executive Summary

The totality of the scientific evidence from adequate and well-controlled trials of COVID-19 convalescent plasma supports that it is safe and effective in the treatment of COVID-19 when sufficiently high titers are used in patients with immunosuppressive disease or receiving immunosuppressive treatments. The risks of CCP are comparable to conventional plasma, and rates and types of transfusion reactions are similar. The sponsor's approach to donor eligibility and product qualification results in CCP with high titers that is likely to retain cross-variant neutralization against circulating strains of SARS-CoV-2. In treatment of patients with COVID-19 and immunosuppressive disease or receiving immunosuppressive treatments, the benefits of CCP are likely to outweigh the risks. I recommend approval of BLA 101766/5169 for licensure of COVID-19 Convalescent Plasma for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatments.

Regulatory History

COVID-19 convalescent plasma is plasma intended for transfusion that is collected from individuals who have recovered from COVID-19, which contains antibodies to SARS-CoV-2. COVID-19 convalescent plasma is a biological product subject to licensure under section 351(a) of the PHS Act. 42 U.S.C. 262(a). COVID-19 Convalescent Plasma is a blood component as defined in 21 CFR 630.3(b).

FDA first issued an Emergency Use Authorization on August 23, 2020, for COVID-19 convalescent plasma (CCP) for the treatment of hospitalized patients with COVID-19. FDA has subsequently reissued the EUA with revisions. Most recently, on December 28, 2021, FDA revised the EUA to limit authorization to the use of CCP with high titers of anti-SARS-CoV-2 antibodies for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment in either the outpatient or inpatient setting. At the time of the 2021 reissuance, the available studies in aggregate supported FDA's determination that that use of COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies may be effective in treating COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment.

Since the most recent reissuance of the EUA for COVID-19 convalescent plasma on December 28, 2021, the epidemiology of SARS-CoV-2, as well as available therapies and vaccines, have continued to evolve. Currently, a large majority of the U.S. population is expected to have detectable antibodies to SARS-CoV-2 by way of vaccination, infection, or both. FDA has approved several therapeutic options for the treatment of COVID-19 in both the outpatient and inpatient settings. As of April 2024, COVID-19 vaccines from three different manufacturers are authorized for emergency use or are FDA-approved.

The COVID-19 pandemic has also seen the emergence of multiple variants of SARS-CoV-2 (Ref.1). Consequently, FDA recognized the potential need for the continued availability of COVID-19 convalescent plasma for certain patient populations with COVID-19. Patients with immunosuppressive disease or receiving immunosuppressive treatments who are infected with SARS-CoV-2 are at greater risk of poor responses to vaccination(Ref.2), prolonged infection (Ref.3), and severe COVID-19 (Ref.4). Passive immune therapy, including COVID-19 convalescent plasma and monoclonal antibodies, can play a role in management of this patient population (Ref.5-7). However, mutations in genomic regions encoding for viral proteins have been shown to negatively impact the expected therapeutic benefit of certain authorized drug products, particularly mAb products that bind to specific epitopes on the receptor binding domain of the SARS-CoV-2 spike protein(Ref.8). Transfusion of COVID-19 convalescent plasma represents an approach to passive immune therapy in patients with immunosuppressive disease or receiving immunosuppressive treatments3 that has the potential to retain activity against circulating SARS-CoV-2 variants when collected from donors with contemporaneous infection with SARS-CoV-2, including donors with a history of both infection and vaccination(Ref.9, 10). Data on the use of COVID-19 convalescent plasma for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatments were reviewed at the time of EUA reissuance in December 2021(Ref.11) Additional studies examining COVID-19 convalescent plasma in immunosuppressive disease or receiving immunosuppressive treatments have subsequently been published and were described in a recent meta-analysis(Ref.12).

In June 2024, FDA issued the guidance document "Recommendations for Investigational and Licensed COVID-19 Convalescent Plasma" (available https://www.fda.gov/media/180209/download and subsequently referred to as "CCP Guidance" in this memo), which noted the regulatory history described above and described FDA's recommendations for licensure of CCP. These recommendations included that sponsors should submit standard operating procedures that describe the criteria used to select donors, the processes to qualify CCP units, and a summary of safety and effectiveness information. FDA also recommended that, based on currently available clinical and scientific evidence, the indication for use for licensed CCP should be the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatments. The sponsor has provided information consistent with those recommendations, which is summarized below.

Summary of Submission

In the current submission, following a series of information requests documented in the submission file, the sponsor provided the following documents relevant to the clinical review:

- COVID-19 Convalescent Plasma Safety and Efficacy Summary
- SOP-1369 (v12) – COVID-19 Convalescent Plasma (CCP) Process
- SOP-1528 (v3) - cPass SARS-CoV-2 Neutralization Antibody Detection Kit, including an addendum that describes their approach to CCP unit qualification
- IFU-326 (v1) – COVID-19 Convalescent Plasma (CCP) Circular of Information

Safety and Effectiveness Information

A document titled "COVID-19 Convalescent Plasma Safety and Efficacy Summary", prepared by David Sullivan, MD with review by Arturo Casadevall, MD and Daniel Hanley, MD is included in the submission. This document summarizes the available data on safety and efficacy for CCP, including the results from several large, adequate, and well-controlled studies in both the inpatient and outpatient setting. Data from several of these studies were considered during issuance of the EUA for CCP, as well as subsequent revisions. Assessment of those data is described in the clinical review memoranda in the submission file for the EUA (Ref.11) and the sponsor points to the evidence summarized in the publicly available clinical review memoranda. The sponsor has also provided additional data and meta-analyses that are described below.

Safety

The sponsor cites safety data from the national Expanded Access program sponsored by the Mayo Clinic and described in published scientific literature(Ref.13). The publication described >100,000 hospitalized subjects with severe of life-threatening COVID-19 who were treated under expanded access, a portion of which were on immunosuppressive therapy (3.8%) or had potentially immunosuppressive comorbidities such as cancer (4.6%). This study was conducted under IND (b) (4) and detailed review of safety reports under the study can be found in the administrative file for that IND. Review of adverse events reported under the IND found that rate of adverse events associated with CCP transfusion were consistent with historical rates of adverse reactions associated with plasma transfusion in hospitalized patients with critical illness. The risks of CCP include those inherent to plasma transfusion such as transfusion related acute lung injury (TRALI), transfusion associated cardiac overload (TACO), allergic/anaphylactic reactions, febrile non-hemolytic transfusion reactions, transfusion-transmitted infections, and hemolytic reactions. Specifically, in the EAP, rates of transfusion reactions are summarized in the figure and table below, adapted from Senefeld et al(Ref.13).

SAE	Possibly related	Probably related	Definitely related	Total	% (n=112,651)
Allergic transfusion reaction	8	21	81	**110**	0.10%
Febrile non-hemolytic transfusion reaction	15	22	10	**47**	0.04%
Hypotensive transfusion reaction	14	5	1	**20**	0.02%
TACO	56	95	12	**163**	0.14%
TRALI	22	14	2	**38**	0.03%
TACO/TRALI	105	110	1	**216**	0.19%
Other transfusion reaction	3	0	0	**3**	0.00%
Total	**223**	**267**	**107**	**597**	0.53%

The sponsor also cites a systematic review and meta-analysis of randomized controlled trials of CCP examining safety outcomes including any adverse reactions, serious reactions, treatment related adverse

reactions, serious treatment related adverse reactions, and venous and arterial thrombotic events(Ref.14). The study included 39 randomized controlled trials enrolling 23,685 subjects. The study found no difference in any rates of any adverse reaction, any serious adverse reaction, serious treatment related adverse reactions, or venous and arterial thrombotic events between CCP treated subjects and controls. There was a slight increase in the rate of any treatment related adverse reaction of any grade (from 2.0% to 3.6%) when comparing CCP to control subjects. The sponsor and study authors attributed this difference to the use of placebo, as no difference was observed in this measure when comparing CCP to control subjects who received FFP. Similar patterns were observed in both the inpatient and outpatient setting. Overall, the incidence of treatment-related serious adverse events following CCP transfusion was low (0.5%) and consistent with data from the EAP summarized above. In review of data from large outpatient studies of CCP during assessment of the EUA, FDA analyses found that the rate of serious transfusion reactions in the outpatient studies was 0.4% overall (ranging 0-1.2% across the studies). This rate is very similar to those reported above.

In a meta-analysis of outpatient studies of CCP, Huaman et al reported an adverse event rate of 5.9%, most of which (4.6%) were consistent with mild allergic transfusion reactions(Ref.15). Adverse events rate were similar between CCP and control plasma, and the investigators reported they did not detect evidence of antibody mediated enhancement of disease. Overall, the data support that CCP has a similar safety profile to conventional plasma for transfusion, including types, rates, and severity of reactions.

Throughout the study of COVID-19 convalescent plasma, there has been theoretical concern regarding the potential for antibody dependent enhancement of disease. As summarized in the review memorandum for the CCP EUA(Ref.11), across several, large randomized controlled trials of CCP, there has been no clear evidence of antibody dependent enhancement of disease due to CCP transfusion. In a post-hoc analysis as part of the CONCOR-1 study (Ref.16), investigators speculated that transfusion of CCP with unfavorable antibody profiles, such as non-functional, non-neutralizing antibodies could be associated with worse clinical outcomes compared to standard care. However, other studies have not observed this phenomenon, and this was only observed with CCP with much lower expected neutralization activity than that produced by the sponsor's proposed approach (see 'Qualification of CCP', below).

There were also early concerns that transfusion of CCP could suppress endogenous host responses to SARS-CoV-2 infection, leading to decreased long-term immunity. However, in outpatient studies of CCP, longitudinal evaluation of antibody levels in CCP transfused subjects compared to non-transfused subjects demonstrated that antibody levels were similar by two weeks after transfusion(Ref.17).

Effectiveness

Studies on the effectiveness of CCP for the treatment of COVID-19, including many randomized, controlled studies in both the inpatient and outpatient setting, were outlined and reviewed as part of the review of the EUA for CCP. That review is documented in the clinical review memoranda associated with the EUA(Ref.11). Additional studies examining COVID-19 convalescent plasma and related therapies in patients with immunosuppressive disease or receiving immunosuppressive treatments, as well as additional data on neutralization titers and cross-variant reactivity in CCP donors, have subsequently been published and are considered below. As noted in the EUA review, CCP has also been the subject of several large meta-analyses. Meta-analyses are challenging to interpret for CCP due to the high heterogeneity in patient populations, concomitant therapies, approaches to manufacture and qualify CCP, evolving epidemiology over the time periods the studies were conducted, and emergence of variants with potential for mismatch in viral strains between donors and recipients. While taking these challenges into consideration, in the current submission, the sponsor cites data from:

- A meta-analysis of five studies conducted in the outpatient setting, each which were also considered during review of the EUA for CCP(Ref.18). Overall, the studies enrolled 2,620 subjects. 12.2% of control subjects and 8.5% of CCP-transfused subjects were hospitalized, resulting in a 3.7% (95% confidence interval [CI], 1.3%–6.0%; P = .001) absolute risk reduction and 30.1% relative risk reduction for all-cause hospitalization. Subgroup analyses suggested that benefits were more likely in those transfused early (within 5 days) and with sufficiently high titers

(defined as equal to or greater than the median neutralization titer for each individual study). While these studies were largely conducted prior to the availability of SARS-CoV-2 vaccination and widespread prior infections and immunity, they support that CCP can be effective in the treatment of SARS-CoV-2 infection.

- A meta-analysis of inpatient studies broken down by the duration of symptoms prior to CCP transfusion, as well as data from observational studies involving matched cohorts. The sponsor's included meta-analyses appear to be drawn from published studies(Ref.19) which included data from 27 randomized, controlled trials representing >18,000 subjects hospitalized with COVID-19. Overall, the investigators determined it was unclear if CCP could decrease mortality compared to controls, with 28-day mortality in control subjects at 22.2% and in treated subjects at 20.2% (RR 0.91 [0.83-1.00], p=0.06). In subgroup analyses, when CCP was transfused within 7 days of symptom onset, the investigators found that CCP reduced the risk of 28-day mortality compared to standard-of-care or placebo controls (RR 0.76 [0.61-0.95]).
- A systematic review and meta-analysis of CCP use in the immunocompromised population including 3 randomized, controlled studies and 5 matched cohort observational studies(Ref.20). The studies included three randomized clinical trials (collectively representing 214 participants), 5 matched cohort studies (n = 1560 participants) and 138 case reports or case series (n = 623 individuals). These studies were analyzed using a standard fixed effects model that compared the observed deaths among patients transfused with CCP with the expected deaths if all patients were equally at risk. The meta-analysis showed an association between CCP use and a mortality benefit in hospitalized, immunocompromised patients with COVID-19. Many case reports on use in immunocompromised patients also described improved viral clearance following CCP transfusion in patients with prior protracted courses of persistent infection despite other treatments. Limitations of the meta-analysis included its lack of individual patient data for the RCT meta-analysis, differences in the volume and titer of CCP used, and how immunocompromise was defined. This reviewer also notes that a large inpatient study of CCP also reported separately on an immunocompromised subgroup(Ref.21), which, while underpowered, suggested larger potential benefits compared to the overall population.

Additional Considerations in Patients with Immunosuppressive Disease or Receiving Immunosuppressive Treatments

The sponsor cites literature explaining that immunocompromised patients are at higher risk for poor outcomes due to SARS-CoV-2 infection and COVID-19, including protracted courses of infection and failure to achieve viral clearance. As noted in the CCP FDA guidance, patients with immunosuppressive disease or receiving immunosuppressive treatments who are infected with SARS-CoV-2 are at greater risk of poor responses to vaccination (Ref.2), prolonged infection (Ref.3), and severe COVID-19 (Ref.4). A recent report estimated that 6.6% of US adults had immunosuppression(Ref.22), either due to immunosuppressive conditions or due to immunosuppressive medications, which was an increase compared to prior estimates. Therefore, this continues to represent an area of need for therapeutic development for COVID-19 (see 'Alternative Therapies', below). For the purposes of the EUA for CCP, FDA authorized CCP for "patients with immunosuppressive disease or receiving immunosuppressive treatments". This description captures the wide range of clinical scenarios where a patient's immunity and ability to form an antibody response might be impaired. Examples include primary immunodeficiencies (e.g., X-linked agammaglobulinemia, common variable immunodeficiency), hematologic malignancy, stem cell transplantation, solid organ transplant, B-cell depleting therapies, comorbidities affecting adaptive immunity (e.g., human immunodeficiency virus), and other immunosuppressive treatments (e.g., certain biologic agents used for autoimmune diseases). Recognizing that studies may not have precisely defined the terms 'immunodeficient' or 'immunocompromised', and that it is difficult to capture the diverse clinical situations in which humoral immunity may be impaired, I concur with the indication language of 'patients with immunosuppressive disease or receiving immunosuppressive treatments' in order to allow the providers to use their clinical judgement to determine whether their patients are likely to have impaired immunity and an increased risk for severe adverse outcomes due to SARS-CoV-2 infection.

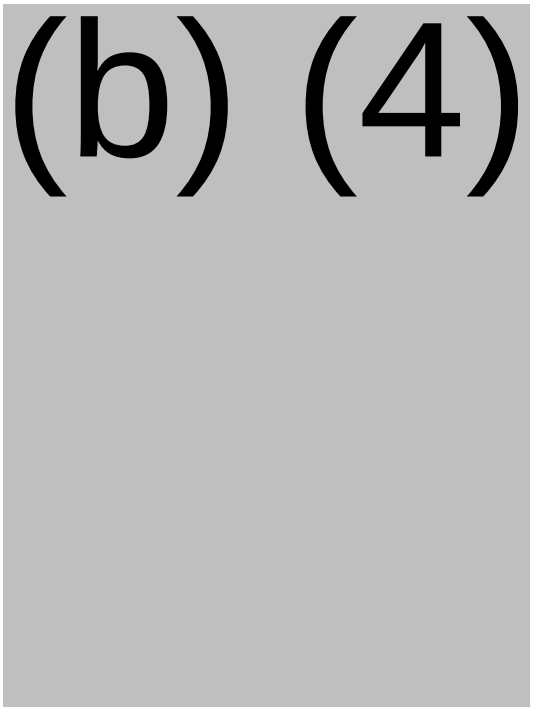
Alternative Therapies

Several monoclonal antibody therapies were previously authorized under EUA for the treatment of COVID-19 in certain patients. However, all authorized therapeutic SARS-CoV-2 antibody products eventually lost activity against circulating variants, and none are currently authorized for the treatment of COVID-19(Ref.23). Pemgarda (pemvibart) is a monoclonal antibody product targeting the SARS-CoV-2 spike protein receptor binding domain that is authorized for pre-exposure prophylaxis of COVID-19 in adults and adolescents who are not currently infected with SARS-CoV-2 and who have moderate-to-severe immune compromise. Authorized or approved antivirals include nirmatrelvir/ritonavir and molnupiravir, which can be taken orally, and remdesivir, which is administered intravenously. Nirmatrelvir/ritonavir can pose challenges due to drug interactions, especially in patients with comorbidities require multiple medical treatments(Ref.24). In addition, a variety of immune modulators are used to treat patients hospitalized with COVID-19. The sponsor cites a review and meta-analysis comparing therapeutic options in the outpatient setting(Ref.25). The study concluded that, despite trial heterogeneity, oral antivirals were the preferred outpatient treatment where available. The study also found that intravenous interventions, including CCP and remdesivir, were also effective, and had advantages in certain settings, particularly for acute and chronic COVID-19 in the immunocompromised. Preparations of anti-SARS-CoV-2 hyperimmune globulin have also been investigated for treatment of COVID-19. While such a product was not effective in treatment of a general population hospitalized with severe COVID-19(Ref.26), a smaller randomized controlled trial in immunocompromised patients did find a clinical benefit(Ref.27). As with CCP, hyperimmune globulin from previously infected and vaccinated donors was also more likely to retain cross-variant neutralization(Ref.28). However, no licensed preparation of anti-SARS-CoV-2 hyperimmune globulin is currently available in the US.

Qualification of CCP

In the July 2024 “CCP guidance, , FDA recommends that sponsors establish their own standard operating procedures that describe the processes used to establish donor eligibility, and COVID-19 convalescent plasma unit qualification. In the current submission, the sponsor established an approach to donor selection and product qualification summarized as follows (information adapted from SOP-1369):

- Donors are not prospectively identified for CCP collection. Instead, all prospective routine donors are asked questions regarding their history of SARS-CoV-2 infection, vaccination, and receipt of monoclonal antibody therapies. Qualifying donors are those who have a history of symptomatic SARS-CoV-2 infection in the last 6 months with a positive diagnostic test, were vaccinated, and were not treated with anti-SARS-CoV-2 monoclonal antibodies.
- If a donor meets the requirements, and successfully donates a plasma product (meeting requirements of SOP-756, SOP-160, and SOP-153), the donation is added to a list for potential manufacture into CCP
- The donation meets the sponsor’s HLA testing requirements
- The donation is tested for neutralizing antibodies using the GenScript cPass assay
- Donations with cPass results showing >80% inhibition are manufactured into CCP



As an addendum to SOP-1528, the sponsor provided data and cited published scientific literature to support their approach to donor eligibility and product qualification. The data support that when there is a history of both prior SARS-CoV-2 infection and vaccination, donors are likely to have higher titers with higher cross-variant neutralization. Note that, in review of the available data, the sponsor refers to antibody levels measured in BAU/mL ('binding antibody units') which is a standardized measure based on correlation to the WHO international standard. One of the studies cited(Ref.29) shows that at a proposed cut-off of 5547 BAU/mL, approximately a quarter of donations met that cutoff and identified all samples with >70% against all omicron sublineages tested. To support the sponsor's approach to qualification, the sponsor provided data from a study in which 4 groups of samples:

- A group of 58 donors qualified according to the sponsor's proposed criteria.
- A group of 98 random donors
- A group of donors from a 2020 sponsor study using alternative criteria
- Two groups of donors from earlier studies of CCP

These data (figure copied above, sponsor's proposed approach is reflected in the group titled '58 Qualified both') demonstrate that the proposed donor qualification and testing approach resulted in CCP with a geometric mean titer of (b) (4) RU/mL in a (b) (4) Note that due to the upper limit of quantification in this test of (b) (4) RU/mL, the sponsor performed additional (b) (4) to measure these titers. Internationally, the labeling for the (b) (4) test allows for conversion from RU/mL to international units. Using the manufacturer's conversion factor of (b) (4) BAU/RU, this means the sponsor's approach would produce CCP with a geometric mean titer of (b) (4) BAU/mL, which is much higher than the current quantitative assay cutoff of 200 BAU/mL in the EUA (Ortho VITROS quantitative test). The sponsor cites several additional studies to support that their approach to donor selection (recently infected, vaccinated donors) results in high-titer CCP that is likely to maintain cross-variant neutralization(Ref.9, 10, 30, 31).

The cPass assay (cPass SARS-CoV-2 Neutralization Antibody Detection Kit, GenScript USA Inc) proposed by the sponsor as a manufacturing test for qualification of high titer CCP is currently authorized under EUA for the semi-quantitative detection of total neutralizing antibodies. This assay is also currently included as an acceptable manufacturing test for CCP under the EUA. The test is based on the ability of anti-SARS-CoV-2 antibodies to block the interaction between the receptor binding domain of the SARS-CoV-2 spike protein and the ACE2 receptor protein. This assay has a positive correlation with live viral neutralization assays, as demonstrated in published scientific literature(Ref.32-34), and in data reviewed by FDA in consideration of manufacturing tests for the manufacture of CCP under EUA.

In the EUA, qualification of CCP as high titer was based on serologic correlates of neutralization activity and thresholds for 'high titer' were established based on the ability of the test to identify products with ID50 neutralization titers of at least 1:250 in a high throughput live viral neutralization test(Ref.35, 36). This neutralization titer threshold was the basis of an FDA analysis comparing outcomes recipients of high (>1:250) versus low (<1:250) titer CCP that showed an association between high titer and improved survival(Ref.37). The studies of CCP summarized above, and in previous consideration of the EUA, used several different methods and cutoffs to define 'high titer' CCP. Subsequent reports have argued that higher titer cutoffs than 1:250 are needed to assure adequate potency in CCP(Ref.38, 39). The data provided by the sponsor demonstrate that the CCP manufactured according to their approach results in

high titer CCP that exceeds the cutoffs used in clinical studies of CCP published to date and the cutoff for high titer used in the EUA.

Circular of Information (COI)

As recommended in FDA guidance, the sponsor provided an addendum to their COI that includes the following sections: product description, actions, indications for use, contraindications, and dosing and administration. Following a series of recommended revisions that are documented in the submission file, the final addendum is labeled as IFU-326, version 1. The information in the COI addendum is accurate and refers to the FDA-recognized COI where appropriate. The submitted labeling is consistent with FDA's expectation for CCP outlined in guidance and provides adequate information and instructions for use for treating providers.

Risk-Benefit Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• COVID-19, caused by SARS-CoV-2 infection, can cause serious illness including respiratory disease, thromboembolic events, cardiomyopathy, neurologic injury, among others. • Immunocompromised patients are at higher risk for severe adverse outcomes after SARS-CoV-2 infection. • SARS-CoV-2 continues to circulate widely in the US and hospitalizations and deaths due to COVID-19 continue to occur, although decreased from pandemic highs. • Vaccination and anti-viral therapies are important for prevention and treatment of COVID-19. • SARS-CoV-2 variants continue to emerge, and while prior immunity due to vaccinations and prior infection remain protective against severe outcomes, the potential for variants capable of escaping immunity remains.	• COVID-19 remains a significant health risk, and SARS-CoV-2 is likely to continue to circulate in the population leading to new variants. • Patients with immunosuppressive disease or receiving immunosuppressive treatments at risk for more severe adverse outcomes and CCP may be an important aspect of their treatment.
Unmet Medical Need	• Although passive immune therapies, such as monoclonal antibodies, were previously shown to be safe and effective and were authorized for treatment of COVID-19, the emergence of variants has resulted in the loss of antibody activity against circulating SARS-CoV-2 strains. • Other treatments (such as small molecule antivirals) are available but may fail to completely clear virus in immunocompromised hosts. • Oral therapies are more readily implemented in clinical practice, but some antiviral therapies (nirmatrelvir/ritonavir) may be limited by their interaction with other medications. • No anti-SARS-CoV-2 hyperimmune globulin product is currently available in the US	• Because high-titer, polyclonal CCP is more likely to retain neutralization activity compared to monoclonal antibody products, and CCP from recently infected individuals is more likely to contain antibodies specific to circulating strains, CCP remains a potentially important therapeutic option for immunocompromised patients.
Clinical Benefit	• High-titer CCP is likely to be effective in reducing mortality and the risk of severe COVID-19 when administered early in the course of illness. • In patients with immunosuppressive disease or receiving immunosuppressive treatments , high-titer CCP appears to improve viral clearance and have a longer therapeutic window for clinical benefit. • Polyclonality of high-titer CCP, and earlier clearance of SARS-CoV-2 may mitigate the emergence or persistence of resistant variants in patients with immunosuppressive disease or receiving immunosuppressive treatments.	• CCP is effective in reducing progression to severe COVID-19 in certain populations. • Patients with immunosuppressive disease or receiving immunosuppressive treatments are likely to experience larger clinical benefit due to their higher risk for severe outcomes. • Patients with immunosuppressive disease or receiving immunosuppressive treatments are likely to have a longer therapeutic window due to impaired ability to generate humoral responses and slow viral clearance.
Risk	• Plasma transfusion is known to have a low rate of transfusion reactions, including allergic reactions, TACO, and TRALI, among others (~0.5-1%). • There were no safety signals for increased risk of thrombotic events due to CCP in well-controlled studies • There is no clear evidence of antibody dependent enhancement of disease or suppression of host immune responses with high-titer CCP • In studies of CCP, transfusion reaction rates for CCP were similar to control plasma and historical rates for plasma transfusion in other settings	• CCP has similar risks to conventional plasma for transfusion. • The low risk of transfusion reactions due to CCP transfusion is more likely to be acceptable when there is a significant risk of severe COVID-19. • Risks of severe COVID-19 in immunocompromised patients are likely to outweigh the low risk of transfusion reaction.
Risk Management	• Transfusion reactions are routinely monitored and reported in clinical practice • The sponsor's approach to donor selection and neutralizing antibody testing is very likely to provide high titer products that minimize the risk of suboptimal antibody composition	• Standard operating procedures for blood component transfusions are adequate to manage the risk of transfusion reactions

Recommendation: I recommend approval of BLA 101766/5169 for licensure of COVID-19 Convalescent Plasma for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatments.

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