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Challenges of conducting clinical trials during the SARS-CoV-2 pandemic: The ASCEND global program experience

Running head: Clinical research during a pandemic

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Abstract

Background and objectives: The coronavirus-19 (COVID-19) pandemic caused substantial morbidity and mortality, straining and disrupting healthcare. Conducting clinical studies in this setting is challenging. The objective of this study was to assess the impact of the pandemic on research activities and implications for study participant and staff safety.

Design, setting, participants, and measurements: The Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat (ASCEND) program includes five phase 3 studies in patients with chronic kidney disease or end stage kidney disease. A survey was administered to site personnel at three of these studies. Results of the survey determined whether changes to study conduct were needed.

Results: Ninety-five percent of sites completed the initial survey (April 13–May 6, 2020), with 3% of sites being temporarily closed and the remaining being open full or part time. Additionally, 75% of sites were able to complete in-clinic study visits in whole or in part, while 16% temporarily converted to telehealth and/or phone visits. Local laboratory values were permitted to inform dosing where on-site Hb could not be assessed, with randomized treatment delivered to participants' homes where possible. Few sites (6%) had participants who changed dialysis facilities, sometimes necessitating a pause in randomized treatment. Most sites reopened by mid-June 2020.

Conclusions: The ASCEND experience highlights lessons on how to mitigate disruption from a pandemic while prioritizing safety of participants and study personnel. Data from these surveys allowed the study team to implement flexible strategies to limit the extent of disruption due to COVID-19 and protect patient safety and trial integrity.

Introduction

The global outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a “public health emergency of international concern” on January 30, 2020 and as a pandemic on March 11, 2020 by the World Health Organization (WHO). The coronavirus-19 (COVID-19) pandemic has had an unprecedented impact on health and healthcare that has affected most of the world to different degrees and at different times. In addition to infecting millions and causing substantial morbidity and mortality, SARS-CoV-2 has strained healthcare systems and caused disruptions to non-COVID-19 related healthcare. Although the premature interruption or disruption of clinical trials is less well recognized, the potential to threaten the development and assessment of new non-COVID-19-related therapeutic agents and approaches will likely have long-term consequences (1–3).

The potential impact of the COVID-19 pandemic on study conduct includes challenges (**Table 1**). The presence and effect of the disruptions outlined in **Table 1** needs to be rapidly identified and addressed in order to preserve the integrity of ongoing studies. The stakes are high, including the protection of trial participants and study personnel from becoming infected with the SARS-CoV-2 virus, and also the safe procurement and administration of study interventions and the challenges of evaluating and adjudicating outcomes when resources are constrained.

Addressing these challenges requires a coordinated effort by investigators, regulators, study sponsors and monitors, study personnel, participants, institutional review boards (IRBs),

ethics committees (ECs), and others. Here, we describe the challenges that arose in a global, phase 3 program that included two cardiovascular outcomes trials (CVOTs) in 41 countries, and the strategies undertaken to safely maintain and adapt the conduct of the studies during the COVID-19 pandemic which was informed by the US Food and Drug Administration (FDA) (4) and the European Medicines Agency (EMA) (5) guidance on the conduct of clinical trials during the pandemic. We describe lessons learned from this experience to inform the research community planning or conducting clinical trials during a pandemic.

Materials and Methods

The Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat (ASCEND) program encompassed five phase 3 trials among patients with chronic kidney disease (CKD) or end stage kidney disease. This paper describes the experience during the pandemic for three of the studies that were sponsored by GlaxoSmithKline (GSK) and conducted by PPD, a contract research organization. Study details are provided in Supplementary Materials.

Survey of study sites about operations during SARS CoV-2

The sponsor developed and administered a questionnaire in collaboration with PPD to assess the impact of the COVID-19 pandemic on ASCEND research activities at clinical sites and how it affected the safety of study participants and staff. Questions covered whether sites were open or temporarily closed and whether study visits and monitoring activities could be completed as usual or with adaptations such as remote visits and/or use of local laboratories

(**Table 2**). Survey data were reviewed by the study team, as well as the steering and executive steering committees who provided ongoing feedback. **Figure 1** shows the global distribution of the active study sites that participated in the initial survey.

Participants receiving in-center HD presented unique study monitoring challenges . Many countries and regions implemented patient cohorting policies, such that patients testing positive for SARS-CoV-2, suspected of having COVID-19, and/or exposed to someone with COVID-19 were moved to specific COVID-19 dialysis facilities to protect non-exposed patients. Following these displaced study participants was not always possible. Thus, the survey included a HD-specific section to be completed by sites participating in ASCEND-ID or ASCEND-D. Sites were asked whether study participants were receiving dialysis in their usual dialysis facilities. When some or all study participants were being treated in different facilities, sites were asked whether study staff were able to have oversight of participants' dialysis treatment, whether personnel at the new dialysis facility were aware that patients were participating in an ASCEND trial, and whether study personnel were able to obtain information about adverse events.

Survey Distribution and Analysis

Surveys were initially disseminated to all active study sites beginning April 13, 2020. Survey data were updated every 2 weeks, then monthly, and then to a targeted dissemination schedule based on COVID-19 rates in the region thereafter. Sites participating in more than one ASCEND study compiled survey responses for each study. For sites with more than one participant in a study, multiple responses could be provided to describe study activities for

different participants; in some cases, sites elected to not answer a question. For these reasons, denominators for survey questions vary slightly. Results of the survey were summarized without formal statistical analyses. Survey results were not part of the trial clinical database. Reported COVID-19 impacts from the survey data were not reconciled to the electronic case report form (eCRF).

Other Study adaptations

Beginning February 24, 2020 in select countries and then globally from March 31, 2020, processes were implemented to ensure continuity of randomized treatment. Where HemoCue Hb could not be assessed, study sites were able to transmit locally-obtained Hb values to PPD medical monitors through a query platform; thereafter, medical monitors advised sites on the appropriate action (increase, decrease, maintain or hold randomized treatment based on the protocol specified dose adjustment scheme). Patient-level study visits and treatments were tracked electronically and summarized monthly. When local Hb values could not be obtained, study participants were temporarily placed on standard of care per local guidance or received no anemia treatment; this information was conveyed to the PPD clinical team by site staff and was summarized accordingly, but data was not collected in a systematic way and may be incomplete.

Results

Survey questions and results are presented in **Table 2**.

Site capabilities based on initial survey (April 13 through May 6, 2020)

Across the three studies ASCEND-D, ASCEND-ID, and ASCEND-ND, 830 unique study sites (some sites participated in more than one study) in 41 countries received a survey between April 13-May 6, 2020. Responses to the initial survey were obtained from 792 sites, hence initial response rate of 95%. This response rate was similar across the three ASCEND studies and across all regions. The survey indicated that 76% of these sites were able to continue operations as usual (no impact from COVID-19), 17% were open part-time, and 3% experienced temporary closure. The Latin America region was most affected, with a 9.5% closure rate (**Table 2A**).

The initial survey interrogated the conduct of study visits among sites for each of the three studies (**Table 2B**). Because many sites participated in more than one ASCEND study, they contributed to responses to each of those studies; 75% reported that they were able to complete study visits according to the study protocol, with 64% completing full study visits, 7% limited to a subset of procedures (e.g., checking a HemoCue Hb), and 4% doing a combination of these. Twenty-one percent of study sites that reported that study visits could not be completed in-clinic according to the protocol. Sixteen percent were able to complete study visits by telephone or telehealth, and <1% were able to travel to participants' homes. In 3% of sites, study visits could not be completed during temporary site closures. Because Hb testing is a key study procedure required to dose-titrate randomized treatment and to monitor for efficacy and safety, ability of the sites to perform point-of-contact measurement of Hb was evaluated. Hb testing was largely performed via HemoCue at the study site or at participants'

homes (66%), whereas 6% of sites relied on testing at a local laboratory, and 10% used some combination of these approaches; 10% reported they were unable to monitor Hb at the time of the initial survey, and the remaining provided a combination of responses or did not answer the question.

Concerning participants who were receiving dialysis, including those who transitioned to dialysis in the ND study, 94% of sites reported that all patients continued to dialyze in their usual outpatient dialysis facilities, 2% reported some patients dialyzing elsewhere (outpatient and/or inpatient), and 4% of sites reported a combination of these, i.e., some subjects dialyzed in usual facility and others elsewhere (**Table 2C**). Overall, for the 20 sites with study participants at new dialysis units, 20% indicated that some patients could not continue randomized treatments. The majority (57%) of these expected to be able to resume randomized treatments when participants were able to return to their usual dialysis facilities.

Use of local Hb values between March 1 and May 6, 2020 and overall

At the participant level, 4224 participants (across all 3 studies) were receiving randomized treatment and monitoring during the period between March 1 and May 6, 2020. Although the majority received study treatment guided by Hb according to the protocol, data summarized from medical monitor queries indicate approximately 3% were able to receive randomized treatment based on Hb results obtained at local laboratories rather than the central study laboratory, with randomized treatment delivered to their homes; this proportion rose to 5% when looking cumulatively from March 1 through August 24, 2020 (**Table 3**). Data

reported by site staff to the PPD clinical team outside of the formal surveys suggest that few participants (<2%) were temporarily converted to standard of care anemia treatment, and this outcome was more likely among ND and ID participants (~3% each) than for the D study (1%). A temporary switch to no anemia treatment was a rare occurrence overall (<1%).

Site status over time

Figure 2 shows the percentage of study sites experiencing closures through September of 2020 overall and by region. Most regions were able to reopen sites between May and mid-June despite varying levels of community spread of COVID-19. This pattern was particularly evident for Latin America, which had more site closures than other regions initially but similar percentages as most other regions by mid-June. Also notable was the Asia Pacific region, which reopened all sites by mid-June and had no further closures, in concordance with a more controlled pandemic in that region. Europe, the Middle East, and Africa followed a different pattern, with few site closures in the initial survey period but a slightly increasing number during the summer and fall.

Discussion

The experience from the ASCEND program during the COVID-19 pandemic demonstrated that despite widespread disruption, the impact on the program was limited. Rapid implementation of actions to assess and mitigate the extent of disruption were responsible for limiting the impact of the pandemic on study centers, research personnel, and

participants. These actions included extensive surveying of sites and rapid analysis of survey data by the scientific and operational leadership of the ASCEND program, which allowed study leadership to provide guidance to sites to adjust study procedures in some cases and adapt them in others.

Survey data were key to evaluating the extent of the disruption. Within weeks of the onset of disruption of healthcare delivery, a detailed survey of site capabilities was developed and disseminated and then repeated regularly. The initial survey response rate was 95% across the three ASCEND studies, and for sites with active subjects, reached 100% by July 13, 2020. Most participants were able to continue in studies and receive randomized treatment according to study protocols. Surveys provided critical information about the extent of disruption and confirmed that disruptions posed by the pandemic were heterogeneous and were related to factors associated with the pandemic itself, as well as with regulatory health-related measures. Thus, nimble and site specific responses had to be implemented to mitigate the effect of the pandemic on the program, with creative solutions that were generated by both study leadership and investigators and personnel from specific study sites.

Survey data were also important in driving modifications of study procedures. Mitigation strategies included conducting study visits remotely in participants' homes, collecting and processing blood samples in a local laboratory or at a participant's home to inform randomized treatment dosing, and using couriers to deliver randomized treatment to participants' homes from study sites. Adjustments to study conduct were relayed through a

series of memos, developed in accordance with guidance from the US FDA (4) and the EMA (5); changes were implemented quickly, and where required, these memos were provided to IRB/ECs.

In some hard-hit areas, sites were temporarily closed because hospital or research facilities were instructed to lockdown and/or study personnel were restricted to working remotely or were deployed elsewhere (e.g., to care for patients with COVID-19 or to support COVID-19 trials) during the pandemic. Thus, study personnel were not available to conduct study visits even in limited form. In addition, some patients were transferred temporarily to facilities where study personnel could not ensure that participants would receive treatment according to study protocols (and would be at risk of receiving duplicative treatment). In these cases, the risk of continuing randomized treatment outweighed the potential benefit, and a small number of participants were temporarily switched to standard of care anemia treatment or to no anemia treatment.

The pattern of anemia treatment varied depending on whether participants were dialysis-dependent or not on dialysis. More participants not receiving dialysis (i.e., participating in ASCEND-ND) had their randomized treatment temporarily interrupted compared with participants who were on dialysis. Temporary site closures in non-dialysis settings were more disruptive to providing randomized treatment because monitoring of Hb was not possible, compared with dialysis settings where routine Hb measurement occurs even outside of study activities. When randomized treatment needed to be temporarily held for patients receiving

dialysis, they were more likely to be switched to standard of care anemia treatment because it was easier to prescribe and administer.

The reasons for temporary site closures and disruptions varied widely by region and country. In some areas, all non-COVID-19-related research was paused to reduce the number of patients coming into clinical centers to minimize exposure to COVID-19 or to allow IRBs/ECs to focus on COVID-19-related studies. In other areas, research nurses were deployed to hospitals or dialysis facilities to care for patients with COVID-19. In some parts of the world, academic centers were converted into COVID-19 treatment facilities so that research participants could not be accommodated.

Complete collection of these adverse events in the eCRFs was critical. Collection of serious adverse events, including MACE, was prioritized. Further, adjudication of the relatedness of deaths and other cardiovascular events to COVID-19 was initiated. In addition, region-specific dates of COVID-19 onset were recorded to allow for pre- and post-COVID-19 'supportive' analyses as advocated by the Heart Failure Association of the European Society of Cardiology and US Food and Drug Administration (4).

The approach used by the ASCEND program during the COVID-19 pandemic had several strengths and some limitations. An important strength was that the survey of site capabilities during the COVID-19 pandemic was disseminated to both operational and scientific leaders and responses returned quickly in real time during the first and subsequent waves of the pandemic.

Second, the high survey response rates of 95% to 100% meant that the surveys were highly representative of what was happening globally. Third, because the safety of participants and personnel was paramount, common interests were identified, making it easier for different layers of study organization to coalesce around this shared goal. Potential limitations included a lack of information about what was happening in the minority of non-responding sites, especially with respect to whether these sites were closed. Despite site closures in the early stages of the pandemic, study sites became more resilient as the pandemic evolved. More sites stayed open and allowed study personnel to perform study procedures, including responding to surveys and implementing mitigation strategies. Indeed, from May to September 2020, the number of temporarily closed sites decreased substantially, and although the disruption has now extended over at least one year, sites have been able to stay open. The reasons for fewer closures were likely a combination of lower rates of COVID-19 over time and better adaptation to COVID-19 when rates were high.

A key lesson learned early during the COVID-19 pandemic for the the ASCEND program was that because COVID-19 would occur in waves or surges that might vary from one country to another or within regions or counties, local and dynamic adaptations to study conduct would be required. For the ASCEND program, in which a large number of participants had already been enrolled, finding safe ways to continue the trial by being nimble allowed for customized responses that prevented pausing the study. Local adaptations were creative and diverse and included conducting study visits via telehealth or by phone. At these sites, remote monitoring

of participants' vital status, collection of adverse effect data or event data was relatively straightforward.

A second important lesson was that the focal point of participant evaluation needed to be flexible. When the HemoCue Hb assessment could not be done, allowing processing and analyzing of blood in local laboratories to inform dosing of randomized treatment was key to success. Evidence that this approach worked was supported by the small percentage of participants whose randomized treatments were discontinued due to the pandemic.

In summary, performing human research during a global pandemic of this proportion raises new practical and ethical challenges as well as patient and personnel safety concerns on a scale never seen before.

Our lessons on mitigating study disruption during a pandemic may assist the wider clinical research community to consider modifying their approach in designing or conducting clinical trials during such situations. In particular, being creative to provide appropriate and flexible solutions to a multiplicity of problems. The overarching guiding principles were the importance of early and continued assessment of site capabilities, the necessity of acting nimbly with site-specific responses given the different patterns and surges of disruptions in different countries. The ultimate goal was always to find the best possible option to provide optimal care for study participants and the best possible actions to protect the integrity of study performance and data collection. Implementation of mitigating strategies that were flexible and targeted limited the extent of disruption to the conduct of the ASCEND trials due to COVID-19.

Disclosures

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AA

RC-R reports scientific consulting and financial support for participation in clinical trials:

AstraZeneca DAPA-CKD trial steering committee, GlaxoSmithKline for ASCEND Investigator and National Leader, Novonordisk: FLOW national leader and investigator. Advisory board member for Boehringer Ingelheim, Amgen, Medtronic, AbbVie. Speaker for AstraZeneca, Janssen, Boehringer Ingelheim, Amgen, Bayer and Sanofi.

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References

1. Psotka MA, Abraham WT, Fiuzat M, Filippatos G, Lindenfeld J, Ahmad T. Conduct of Clinical Trials in the Era of COVID-19: JACC Scientific Expert Panel. *J Am Coll Cardiol*. 76(20): 2368-2378, 2020.
2. Siontis GC, Sweda R, Windecker S. Cardiovascular clinical trials in the era of a pandemic. *J Am Heart Assoc*. 9(20): e018288, 2020.
3. Tuttle KR. Impact of the COVID-19 pandemic on clinical research. *Nat Rev Nephrol*. 16(10): 562-564, 2020.
4. Food and Drug Administration guidance on conduct of clinical trials of medical products during COVID-19 public health emergency (March 2020). Guidance for industry, investigators, and institutional review boards. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency>
5. European Medicines Agency guidance to sponsors on how to manage clinical trials during the COVID-19 pandemic EMA/141885/2020. <https://www.ema.europa.eu/en/news/guidance-sponsors-how-manage-clinical-trials-during-covid-19-pandemic>

6. Singh AK, Blackorby A, Cizman B, Carroll K, Cobitz AR, Davies R, et al. Study design and baseline characteristics of patients on dialysis in the ASCEND-D trial. *Nephrol Dial Transplant*. 2021; gfab065, <https://doi.org/10.1093/ndt/gfab065>. Online ahead of print.

7. World Health Organization. Global Surveillance for human infection with coronavirus disease (COVID-19). Updated 20 March 2020. [https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-\(2019-ncov\)](https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov))

Tables

Table 1. Potential Challenges to Study Conduct

<p>Operational challenges</p> <ul style="list-style-type: none">• Reassignment of study staff to COVID-19 units or COVID-19 trials• Travel limitations for participants and personnel to study sites• Interruptions to the supply chain for investigational products• Site closures
<p>Safety challenges</p> <ul style="list-style-type: none">• Quarantine and/or sickness of participants and study staff• Study participants' fear of contracting the virus by travel to the sites• Infection of study participants with SARS-CoV-2
<p>Analytical challenges</p> <ul style="list-style-type: none">• Difficulties with data and sample collection• Statistical complexity of handling missing data

Table 2. Results of the Initial ASCEND Site Survey (April 13 through May 6, 2020)

A. Study site status overall and by region					
Q1. Is the study site opened, temporarily closed, or open part time?	Global	APAC	EMEA	LA	NA
	N=830	N=171	N=326	N=74	N=259
Open full time	76%	75%	86%	66%	66%
Open part time	17%	20%	10%	24%	22%
Temporarily closed	3.0%	3.5%	1.2%	9.5%	3.1%
No response from site	4.6%	1.2%	3.7%	0%	9.3%
B. Impact on conducting study visits by study site staff who responded to initial survey¹					
	Overall	ASCEND-ND	ASCEND-ID	ASCEND-D	
Q2. Are site staff able to complete patient visits as per protocol?	N=1113	N=566	N=108	N=439	
Yes	75%	71%	72%	81%	
Full study visits	64%	59%	63%	70%	
Limited to a subset of procedures	7.0%	7.2%	8.3%	6.4%	
Combination of full/limited study visits	3.6%	3.9%	0.9%	3.9%	
No response given	0.6%	0.5%	0%	0.9%	
No	21%	25%	21%	16%	
ONLY By telephone or telehealth	16%	19%	11%	13%	
ONLY At participants' homes	0.4%	0.5%	0%	0%	
No remote visits completed	3.3%	3.7%	10%	1.1%	
Combinations of above	1.0%	1.4%	0	0.7%	
No response given	0.6%	0.9%	0%	0.5%	
No response given	4.0%	3.9%	6.5%	3.4%	
Q3. Is hemoglobin being checked?	N=1053	N=531	N=105	N=417	
Yes, at the study site / participants' homes	66%	63%	62%	71%	
Yes, at a local laboratory	5.7%	7.0%	6.7%	3.8%	
Combinations of Yes responses ²	9.5%	10%	5.7%	9.8%	
No	10%	11%	17%	7.4%	
Combinations of Yes and No responses ²	2.8%	3.2%	1.9%	2.4%	
No response given	5.9%	6.0%	6.7%	5.5%	
Q4. Is the research office able to accept randomized treatment supply samples as normal?	N=1053	N=531	N=105	N=417	
Yes	89%	89%	87%	90%	
No	5.5%	6.6%	6.7%	3.8%	
No response given	5.6%	4.7%	6.7%	6.5%	
Q5. Is the site able to ship lab samples to central lab?	N=1053	N=531	N=105	N=417	

Yes	84%	83%	81%	86%
No	11%	13%	13%	8.2%
No response given	5.0%	4.5%	5.7%	5.5%
Q6. If site cannot ship lab samples to central lab: Does the site have the ability to store frozen samples?				
	N=116	N=68	N=14	N=34
Yes	63%	68%	36%	65%
No	29%	25%	50%	29%
No response given	7.8%	7.4%	14%	5.9%
C. Impact on dialysis participants by study site staff who responded to initial survey¹				
Q7. Are study participants being dialyzed at their regular dialysis facilities?				N=718
Yes				94%
No				1.8%
Combination of yes and no responses ²				3.9%
Q8. For sites where study participants have changed sites: Are the study staff still able to have oversight of participants' dialysis?				N=41
Yes				51%
No				12%
Yes, for some participants but not all				22%
No response given				15%
Q9. For sites where "oversight" is in question: Are the staff at the new units aware that the patients are participating in ASCEND?				N=20
Yes				30%
No				30%
Combination of yes and no responses ²				10%
No response given				30%
Q10. For sites with study participants at new dialysis units: Are the staff having difficulty obtaining information about participants, including AE/SAE?				N=41
Yes				15%
No				59%
Combination of yes and no responses ²				20%
No response given				7.3%
Q11. For sites with study participants at new dialysis units: Are participants able to continue randomized treatment?				N=41
Yes				59%
No				20%
Combination of yes and no responses ²				15%
No response given				7.3%
Q12. For sites with study participants at new dialysis units where randomized treatment could not be continued: Is there a possibility that they will resume randomized treatment when they return to regular dialysis units?				N=14
Yes				57%
No				21%
No response given				21%

Percentages <10% presented to one decimal place; >10% rounded to nearest whole number therefore, response tallies may >100%.

N=the number of site staff contacted.

¹Only Research sites that had patients on dialysis were included.

²For “Combination of yes and no responses”, sites had study participants that aligned with each of these responses.

AE, adverse event; APAC, Asia Pacific; EMEA, Europe Middle East Africa; LA, Latin America; NA, North America; SAE, severe adverse event.

APAC = Australia, India, Hong Kong, Malaysia, New Zealand, Philippines, South Korea, Singapore, Taiwan, Thailand, Vietnam.

EMEA = Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Italy, Israel, Netherlands, Norway, Poland, Portugal, Romania, Russia, South Africa, Spain, Sweden, Turkey, Ukraine, United Kingdom.

LA = Argentina, Brazil, Columbia, Mexico.

NA = Canada, United States of America.

Table 3. Patient-level Randomized Treatment Outcomes

	Expected # of dispensings of RT per protocol ¹		Continue RT, dispensed based on Hb from local lab (%) ²	
	Initial	Cumulative	Initial	Cumulative
ASCEND-ND	2,861	7,890	4.1%	7.2%
ASCEND-ID	111	162	1.8%	3.1%
ASCEND-D	2,640	6,785	1.1%	2.3%
Total	5,612	14,837	2.7%	4.9%

D, Dialysis study; Hb, hemoglobin; ID, Incident Dialysis study; ND, Non-dialysis study; RT, randomized treatment

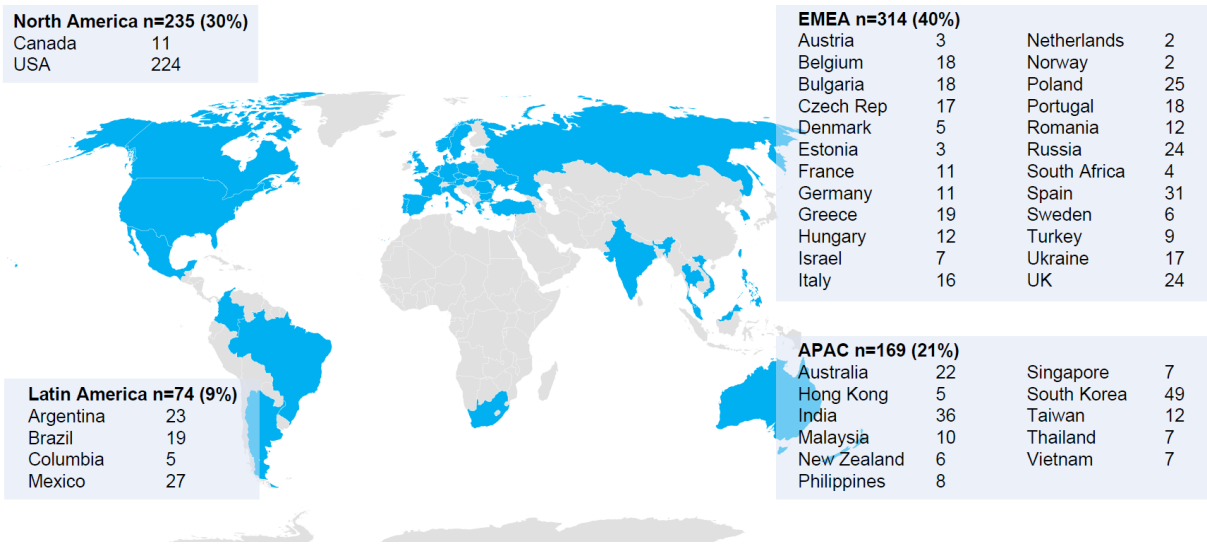
Initial = March 01, 2020 through May 6, 2020; Cumulative = March 1, 2020 through August 24, 2020

¹Data reported by Interactive Response Technology system

²Data reported via queries to Medical Monitors

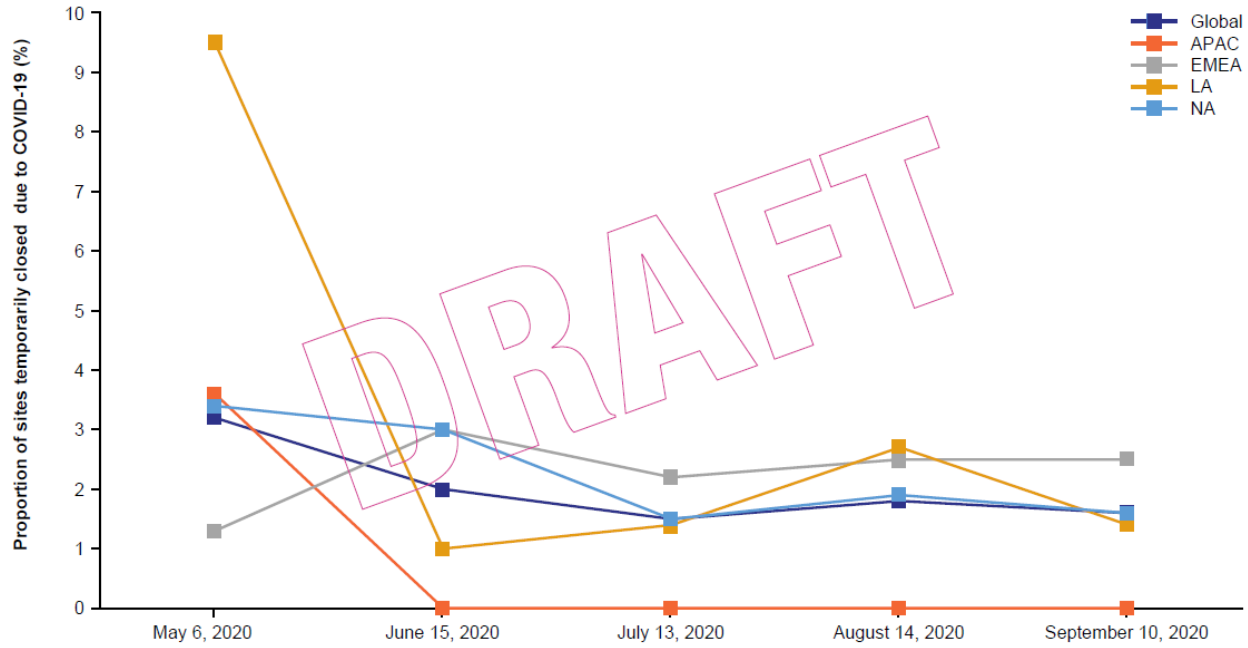
Figures

Figure 1. Global Distribution of Study Sites for ASCEND-ND, ID, D Studies that Participated in the Initial Survey



APAC, Asia Pacific ; EMEA, Europe, Middle East, Africa

Figure 2. Proportion of Sites that were Temporarily Closed due to COVID-19



APAC, Asia Pacific = Australia, India, Hong Kong, Malaysia, New Zealand, Philippines, South Korea, Singapore, Taiwan, Thailand, Vietnam

EMEA, Europe, Middle East, Africa = Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Italy, Israel, Netherlands, Norway, Poland, Portugal, Romania, Russia, South Africa, Spain, Sweden, Turkey, Ukraine, United Kingdom

LA, Latin America = Argentina, Brazil, Columbia; Mexico

NA, North America = Canada, United States of America

Supplemental Materials for:

Challenges of conducting clinical trials during the SARS-CoV-2 pandemic: The ASCEND global program experience

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ASCEND studies

ASCEND-ND (NCT02876835) is an ongoing CVOT enrolling patients with CKD not requiring dialysis treatment, ASCEND-D (NCT02879305) was a CVOT that enrolled patients receiving maintenance hemodialysis (HD) or peritoneal dialysis (PD), and ASCEND-ID (NCT03029208) was a 52-week study that enrolled incident HD or PD patients. All three are open-label (sponsor-blind), randomized controlled trials of daprodustat vs. recombinant human erythropoietin (rhEPO).

Participants in ASCEND-ND were adults with CKD stage 3 to 5 who had anemia (hemoglobin [Hb] 8-10 g/dL for those not using erythropoietin stimulating agents [ESAs] and 8–11 g/dL for prior ESA users). ASCEND-ID participants were patients who were initiating dialysis with anemia (Hb 8–11 g/dL) but had not been receiving ESAs, aside from limited use as part of dialysis initiation. ASCEND-D enrolled prevalent dialysis patients with anemia treated with ESAs (Hb 8–11.5 g/dL); design and baseline characteristics have been previously published (6). Across

all studies, participants were not iron deficient (based on serum ferritin >100 ng/mL and transferrin saturation >20%).

Participants were randomly assigned to receive daily oral daprodustat or rhEPO (ASCEND-D: intravenous [IV] epoetin alfa for those on HD or subcutaneous [SC] darbepoetin alfa for those on PD; and ASCEND-ID and ND: SC/IV darbepoetin alfa). Randomized (study) treatments were titrated to achieve and maintain Hb between 10 and 11 g/dL during a 28-week titration period and a maintenance period from week 28 through the end of the study. All three trials had a primary endpoint of mean change in Hb between the baseline and efficacy period (mean over weeks 28–52), while the CVOTs had an additional (co-primary) endpoint of time to first occurrence of an adjudicated major cardiovascular event (MACE), a composite of all-cause mortality, non-fatal myocardial infarction, and non-fatal stroke.

ASCEND-D recruited 2964 participants from September 28, 2016 to June 15, 2018, had participants receiving randomized treatment after the onset of the COVID-19 pandemic, and completed the last study visit in November 2020; ASCEND-ID enrolled 312 participants between May 11, 2018 and July 22, 2019, with the last study visit on September 24, 2020. ASCEND-ND enrolled 3872 participants from September 27, 2016 through September 25, 2020 which included enrollment during the pandemic, with follow-up concluded in April 2021.

Routine study operations involved participant visits at least every 4 weeks during the titration and efficacy phases of the study (4–52 weeks), and for the CVOTs, at least every 12

weeks after week 52 until the end of study. During these visits, blood was drawn for Hb determination by a central laboratory for efficacy assessments, and point-of-care Hb testing (HemoCue, Angelholm, Sweden) was performed in order to titrate study medications to maintain Hb in the target range. Additional blood samples were sent to a central laboratory for routine safety evaluations, as well as for future analysis of biomarkers.

COVID-19 Data Collection and Impact

The sponsor and the independent steering committees recognized the importance of collecting detailed information about COVID-19 and related clinical events early in the pandemic. On March 31, 2020, sites were instructed to complete a COVID-19 infection electronic case report form (eCRF) using the WHO case definitions (suspected, probable, and confirmed cases) (4,7), in addition to routine (serious) adverse event reporting through normal reporting mechanisms. On August 25, 2020, new eCRF questions were added to study visits, as well as to the Investigational Product Discontinuation and Study Conclusion forms, to capture details about the impact on visits, visit assessments, and treatment interruptions related to COVID-19. Finally, deviations because of COVID-19 were collected. In addition, during the pandemic, the clinical events classification group led by the Duke Clinical Research Institute adjudicated relatedness of clinical events to COVID-19 as well as cause of death due to COVID-19. These results will be available at the end of the studies and will inform the scientific community and regulators about the potential impact of COVID-19 on different types of clinical outcomes, cause of death, and overall trial event rates.