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

**DOI:** 10.34067/KID.0006212021


**Key Points:**
*The COVID-19 pandemic has had an unprecedented impact on health and healthcare, and posed challenges to the conduct of clinical trials*

*Targeted mitigating strategies, based on early and continued data collection from site surveys, limited disruption to the ASCEND trials*

*Flexibly allowing Hb assessment at local laboratories to inform randomized treatment dosing was key to limiting treatment discontinuations*

**Abstract:**

**Disclosures:** KLJ reports consultancy fees from GlaxoSmithKline. AA reports consultancy fees from GlaxoSmithKline. 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. ID reports research grants from Medtronic and Sanofi-Genzyme and advisory board member for GlaxoSmithKline and AstraZeneca. VK reports local India consultancy agreements with Torrent Pharmaceuticals, Novartis, Roche, Panacea, Sanofi Aventis, Intas pharmaceuticals, Biocon Pharmaceuticals, GlaxoSmithKline, RPG Life Sciences and AstraZeneca. Research funding from Novartis India, Sanofi Aventis India, Astellas India. Honoraria from Novartis, India; Roche India; Astellas, India; Torrent, India; Reddy's India; Intas India and JB Pharmaceuticals India. Scientific advisor for Roche, India; Novartis, India; Torrent; Sanofi Aventis; Reddy's India, Biocon India; Medtronic; Wockhardt, India. Speakers Bureau for Novartis, India; Roche, India; Panacea, India; Sanofi Aventis, India; Intas, India; Biocon, India; Pfizer; Johnson and Johnson; JB pharmaceuticals; AstraZeneca, India. RDL reports grants and personal fees from Bristol-Myers Squibb and Pfizer, personal fees from Boehringer Ingelheim and Bayer AG and research grants from Amgen Inc, GlaxoSmithKline, Medtronic PLC, and Sanofi Aventis. BR reports honoraria for CME talks from Servier, AstraZeneca, Boehringer Ingelheim, Sandoz, Merck and Novartis, and has served on a Servier Advisory Board. AKS reports consultation fees from ProKidney, Novartis, Retrophin, Goldfinch Bio, Reata, Ardelyx, Boehringer Ingelheim, Bayer AG and DiaMedica; consultancy fees from ProKidney, Novartis, Boehringer Ingelheim, Reata and Ardelyx; speaker bureau AstraZeneca, Aurinia and Amgen AKS reports consultation fees from GlaxoSmithKline. LM, OMVN, MO, HT have no conflicts to disclose. BC, ARC, AMM are employees of and stockholders in GlaxoSmithKline.

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Author Contributions: Kirsten Johansen: Conceptualization; Writing - original draft; Writing - review and editing Anjali Acharya: Conceptualization; Writing - review and editing Borut Cizman: Conceptualization; Writing - review and editing Alexander Cobitz: Conceptualization; Writing - review and editing Ricardo Correa-Rotter: Conceptualization; Writing - review and editing Indranil Dasgupta: Conceptualization; Writing - review and editing Vijay Kher: Conceptualization; Writing - review and editing Renato Lopes: Conceptualization; Writing - review and editing Leonardo Matsumoto: Conceptualization; Writing - review and editing Amy Meadowcroft: Conceptualization; Writing - original draft; Writing - review and editing Osvaldo Merege Vieira Neto: Conceptualization; Writing - review and editing Marilu Okabe: Conceptualization; Writing - review and editing Brian Rayner: Conceptualization; Writing - review and editing Arnold Silva: Conceptualization; Writing - review and editing Hilary Thomas: Conceptualization; Writing - review and editing Ajay Singh: Conceptualization; Writing - original draft; Writing - review and editing

Data Sharing Statement: Partial restrictions to the data and/or materials apply (please include a detailed explanation): Anonymized individual patient data and study documents can be requested for further research from https://www.clinicalstudydatarequest.com/.

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

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Key points

- The COVID-19 pandemic has had an unprecedented impact on health and healthcare, and posed challenges to the conduct of clinical trials
- Targeted mitigating strategies, based on early and continued data collection from site surveys, limited disruption to the ASCEND trials
- Flexibly allowing Hb assessment at local laboratories to inform randomized treatment dosing was key to limiting treatment discontinuations

Introduction

The coronavirus-19 (COVID-19) pandemic has had an unprecedented impact on health and healthcare. Severe acute respiratory syndrome coronavirus 2 (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, it has the potential to threaten the development of new non-COVID-19-related therapies. (1–3).

Study disruptions need to be rapidly identified and addressed to preserve the integrity of ongoing studies and design of new ones. Here, we describe the challenges that arose in three global Phase 3 trials and the strategies undertaken to safely maintain and adapt the conduct of the studies during the COVID-19 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, of which three were sponsored by GlaxoSmithKline (GSK) and conducted by Pharmaceutical Product Development
Study details for the non-dialysis (ASCEND-ND, NCT028768355), dialysis (ASCEND-D, NCT02879305) and incident dialysis (ID, NCT03029208) are provided in the Supplemental 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 (complete survey is provided in Supplemental Materials). 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. Furthermore, dialysis-specific questions were used to determine if participants were treated in their usual or different dialysis facilities, and the challenges of the latter in conducting the trials.

Survey distribution and analysis

Surveys were disseminated to active study sites beginning April 13, 2020. Survey data were updated every 2 weeks, then monthly, and thereafter on a targeted basis depending on COVID-19 rates in the region. For sites with more than one participant in a study, multiple responses could be provided to describe study activities for participants. For these reasons, denominators for survey questions vary slightly. Survey results were not part of the trial clinical database, and data were not reconciled to the electronic case report forms.

Other study adaptations

Beginning February 24, 2020, processes were implemented to ensure continuity of randomized treatment. Where HemoCue hemoglobin (Hb) could not be assessed, study sites were able to
transmit locally-obtained Hb values to PPD through a query platform. When local Hb values could not be obtained, participants were temporarily placed on standard of care or received no anemia treatment.

**Results**

Key survey questions and results are presented in Table 1.

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

Across ASCEND-D, ASCEND-ID and ASCEND-ND, 830 unique study sites in 41 countries received a survey between April 13-May 6, 2020 (Figure 1). Responses to the initial survey were obtained from 792 sites (95% response rate) and reached 100% by July 13, 2020.

Because many sites participated in more than one ASCEND study, they contributed responses to each study; 75% reported that they were able to complete study visits per protocol, with 64% completing all procedures and 7% limited to a subset of procedures (Table 1A). Twenty-one percent of study sites reported that study visits could not be completed in-clinic. 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. Hb testing was largely performed via HemoCue at the study site or at participants’ homes (66%) or at a local laboratory (6%) or some combination of these approaches (10%); 10% reported they were unable to monitor Hb at the time of the initial survey.

Ninety-four percent of sites reported that all patients receiving dialysis continued to dialyse in their usual facilities, 2% reported some patients dialysing elsewhere, and 4% a combination of
the two (Table 1B). Overall, for the sites with participants at new dialysis units, 20% indicated that some patients could not continue randomized treatments.

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

At the participant level, 4224 participants (across all 3 studies) were receiving randomized treatment and monitoring between 1 March and 6 May 2020. Although the majority received study treatment guided by Hb according to the protocol, approximately 3% received randomized treatment based on Hb results obtained at local laboratories, with randomized treatment delivered to their homes; this rose to 5% when looking cumulatively from 1 March to 24 August 2020 (Table 2). Few participants (<2%) were temporarily converted to standard of care anemia treatment, and this outcome was more likely among non-dialysis and incident dialysis participants (~3% each) than for the D study (1%). A temporary switch to no anemia treatment was a rare occurrence (<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 by mid-June.
Discussion

Despite widespread disruption during the COVID-19 pandemic, the impact on the ASCEND trials was limited. Extensive surveying of sites within weeks of the onset of the pandemic and rapid analysis of survey data allowed study leadership to provide guidance to sites to adjust and adapt study procedures. This limited the impact of the pandemic on study centers, research personnel and participants.

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.

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. In addition, some participants were transferred temporarily to facilities where study personnel could not ensure they would receive treatment according to study protocols. 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.

Nevertheless, most participants were able to continue to receive randomized treatment according to study protocols. More participants not receiving dialysis had their randomized treatment temporarily interrupted than 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.

The approach used by the ASCEND trials during the COVID-19 pandemic had several strengths and some limitations. An important strength was that survey data was disseminated to operational and scientific leaders in real time during the first and subsequent waves of the pandemic to enable mitigation strategies to be developed and employed. Second, the high survey response rates of 95% to 100% meant that the surveys were highly representative of what was happening globally. 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. Indeed, from May to September 2020, the number of temporarily closed sites decreased substantially. The reasons for fewer closures were likely a combination of lower rates of COVID-19 over time and better adaptation to COVID-19 even when rates were high.

A key lesson learned early during the COVID-19 pandemic for the ASCEND trials was that because COVID-19 occurred in waves that varied across regions and countries, adaptations to study conduct were required. Finding safe ways to continue the trial were creative and diverse and included conducting study visits by telephone or telehealth.

A second important lesson was that Hb assessment needed to be flexible. When the HemoCue Hb assessment could not be done at study sites, allowing Hb assessment at local laboratories to inform dosing of randomized treatment was key to success as evidenced by the small percentage of participants whose randomized treatments were discontinued.
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. The overarching guiding principles were the importance of early and continued assessment of site capabilities and the necessity to act nimbly with site specific responses given different patterns and surges of disruptions in different countries. The ultimate goal was to provide optimal care for participants while protecting 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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Author contributions

Kirsten Johansen: Conceptualization; Writing - original draft; Writing - review and editing. Anjali Acharya: Conceptualization; Writing - review and editing. Borut Cizman: Conceptualization; Writing - review and editing. Ricardo Correa-Rotter: Conceptualization; Writing - review and editing. Indranil Dasgupta: Conceptualization; Writing - review and editing. Vijay Kher: Conceptualization; Writing - review and editing. Renato Lopes: Conceptualization; Writing - review and editing. Leonardo Matsumoto: Conceptualization; Writing - review and editing. Amy Meadowcroft: Conceptualization; Writing - original draft; Writing - review and editing. Osvaldo Merege Vieira Neto: Conceptualization; Writing - review and editing. Marilu Okabe: Conceptualization; Writing - review and editing. Brian Rayner: Conceptualization; Writing - review and editing. Arnold Silva: Conceptualization; Writing - review and editing. Hilary Thomas: Conceptualization; Writing - review and editing. Ajay Singh: Conceptualization; Writing - original draft; Writing - review and editing. All authors contributed to the data analysis or interpretation, critically reviewed the manuscript and approved the final version for submission.

Data sharing statement

Partial restrictions to the data and/or materials apply. Anonymized individual patient data and study documents can be requested for further research from https://www.clinicalstudydatarequest.com/.

Supplemental materials

Brief description of ASCEND studies
Complete Survey Administered to Sites

References


Table 1. Results of the Initial ASCEND Site Survey (April 13 through May 6, 2020)

A. Impact on conducting study visits by study site staff who responded to initial survey

<table>
<thead>
<tr>
<th>Are site staff able to complete patient visits as per protocol?</th>
<th>Overall</th>
<th>ASCEND-ND</th>
<th>ASCEND-ID</th>
<th>ASCEND-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>N=1113</td>
<td>N=566</td>
<td>N=108</td>
<td>N=439</td>
</tr>
<tr>
<td>Full study visits</td>
<td>75%</td>
<td>71%</td>
<td>72%</td>
<td>81%</td>
</tr>
<tr>
<td>Limited to a subset of procedures</td>
<td>64%</td>
<td>59%</td>
<td>63%</td>
<td>70%</td>
</tr>
<tr>
<td>Combination of full/limited study visits</td>
<td>7.0%</td>
<td>7.2%</td>
<td>8.3%</td>
<td>6.4%</td>
</tr>
<tr>
<td>No response given</td>
<td>0.6%</td>
<td>0.5%</td>
<td>0%</td>
<td>0.9%</td>
</tr>
<tr>
<td>No</td>
<td>21%</td>
<td>25%</td>
<td>21%</td>
<td>16%</td>
</tr>
<tr>
<td>ONLY By telephone or telehealth</td>
<td>16%</td>
<td>19%</td>
<td>11%</td>
<td>13%</td>
</tr>
<tr>
<td>ONLY At participants’ homes</td>
<td>0.4%</td>
<td>0.5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>No remote visits completed</td>
<td>3.3%</td>
<td>3.7%</td>
<td>10%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Combinations of above</td>
<td>1.0%</td>
<td>1.4%</td>
<td>0</td>
<td>0.7%</td>
</tr>
<tr>
<td>No response given</td>
<td>0.6%</td>
<td>0.9%</td>
<td>0%</td>
<td>0.5%</td>
</tr>
<tr>
<td>No response given</td>
<td>4.0%</td>
<td>3.9%</td>
<td>6.5%</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Is hemoglobin being checked?</th>
<th>Overall</th>
<th>ASCEND-ND</th>
<th>ASCEND-ID</th>
<th>ASCEND-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes, at the study site/participants’ homes</td>
<td>N=1053</td>
<td>N=531</td>
<td>N=105</td>
<td>N=417</td>
</tr>
<tr>
<td>Yes, at a local laboratory</td>
<td>66%</td>
<td>63%</td>
<td>62%</td>
<td>71%</td>
</tr>
<tr>
<td>Combinations of Yes responses²</td>
<td>9.5%</td>
<td>7.0%</td>
<td>6.7%</td>
<td>3.8%</td>
</tr>
<tr>
<td>No</td>
<td>10%</td>
<td>10%</td>
<td>5.7%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Combinations of Yes and No responses²</td>
<td>2.8%</td>
<td>3.2%</td>
<td>1.9%</td>
<td>2.4%</td>
</tr>
<tr>
<td>No response given</td>
<td>5.9%</td>
<td>6.0%</td>
<td>6.7%</td>
<td>5.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Is the research office able to accept randomized treatment supply samples as normal?</th>
<th>Overall</th>
<th>ASCEND-ND</th>
<th>ASCEND-ID</th>
<th>ASCEND-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>N=1053</td>
<td>N=531</td>
<td>N=105</td>
<td>N=417</td>
</tr>
<tr>
<td>No</td>
<td>89%</td>
<td>89%</td>
<td>87%</td>
<td>90%</td>
</tr>
<tr>
<td>No response given</td>
<td>5.5%</td>
<td>6.6%</td>
<td>6.7%</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Is the site able to ship lab samples to central lab?</th>
<th>Overall</th>
<th>ASCEND-ND</th>
<th>ASCEND-ID</th>
<th>ASCEND-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>N=1053</td>
<td>N=531</td>
<td>N=105</td>
<td>N=417</td>
</tr>
<tr>
<td>No</td>
<td>84%</td>
<td>83%</td>
<td>81%</td>
<td>86%</td>
</tr>
<tr>
<td>No response given</td>
<td>11%</td>
<td>13%</td>
<td>13%</td>
<td>8.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If site cannot ship lab samples to central lab: Does the site have the ability to store frozen samples?</th>
<th>Overall</th>
<th>ASCEND-ND</th>
<th>ASCEND-ID</th>
<th>ASCEND-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>N=116</td>
<td>N=68</td>
<td>N=14</td>
<td>N=34</td>
</tr>
<tr>
<td>No</td>
<td>95%</td>
<td>97%</td>
<td>97%</td>
<td>91%</td>
</tr>
<tr>
<td>No response given</td>
<td>5.0%</td>
<td>4.5%</td>
<td>5.7%</td>
<td>5.5%</td>
</tr>
</tbody>
</table>
### B. Impact on dialysis participants by study site staff who responded to initial survey¹

<table>
<thead>
<tr>
<th>Are study participants being dialyzed at their regular dialysis facilities?</th>
<th>N=718</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>63%</td>
</tr>
<tr>
<td>No</td>
<td>29%</td>
</tr>
<tr>
<td>No response given</td>
<td>7.8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>For sites where study participants have changed sites: Are the study staff still able to have oversight of participants’ dialysis?</th>
<th>N=41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>68%</td>
</tr>
<tr>
<td>No</td>
<td>25%</td>
</tr>
<tr>
<td>No response given</td>
<td>7.4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>For sites where “oversight” is in question: Are the staff at the new units aware that the patients are participating in ASCEND?</th>
<th>N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>36%</td>
</tr>
<tr>
<td>No</td>
<td>50%</td>
</tr>
<tr>
<td>No response given</td>
<td>14%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>For sites with study participants at new dialysis units: Are the staff having difficulty obtaining information about participants, including AE/SAE?</th>
<th>N=41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>36%</td>
</tr>
<tr>
<td>No</td>
<td>25%</td>
</tr>
<tr>
<td>No response given</td>
<td>14%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>For sites with study participants at new dialysis units: Are participants able to continue randomized treatment?</th>
<th>N=41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>65%</td>
</tr>
<tr>
<td>No</td>
<td>29%</td>
</tr>
<tr>
<td>No response given</td>
<td>5.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>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?</th>
<th>N=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>36%</td>
</tr>
<tr>
<td>No</td>
<td>50%</td>
</tr>
<tr>
<td>No response given</td>
<td>14%</td>
</tr>
</tbody>
</table>

Percentages <10% presented to one decimal place; >10% rounded to nearest whole number therefore, response tallies may be >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 participants that aligned with each of these responses.

AE, adverse event; SAE, serious adverse event.
### Table 2. Patient-level Randomized Treatment Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Expected no. of dispensings of RT per protocol</th>
<th>Continue RT, dispensed based on Hb from local lab (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Cumulative</td>
</tr>
<tr>
<td><strong>ASCEND-ND</strong></td>
<td>2861</td>
<td>7890</td>
</tr>
<tr>
<td><strong>ASCEND-ID</strong></td>
<td>111</td>
<td>162</td>
</tr>
<tr>
<td><strong>ASCEND-D</strong></td>
<td>2640</td>
<td>6785</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>5612</td>
<td>14,837</td>
</tr>
</tbody>
</table>

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

1 Data reported by Interactive Response Technology system.

2 Data reported via queries to Medical Monitors.

D, Dialysis study; Hb, hemoglobin; ID, Incident Dialysis study; ND, Non-dialysis study; RT, randomized treatment.
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.
Challenges of conducting clinical trials during the SARS-CoV-2 pandemic: The ASCEND global program experience


Brief description of ASCEND studies

ASCEND-ND (NCT02876835) is an ongoing cardiovascular outcome trial (CVOT) enrolling patients with chronic kidney disease (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 versus 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 (1). Across all
Participants were randomly assigned to receive daily oral daporodustat 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, 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.

References

Complete Survey Administered to Sites

QUESTIONS:

1. Questionnaire completion date: ______

2. Region: ______

3. Site Country: ______

4. Site #s (only complete multiple numbers if the sites have the same PI AND the answers are the same across all studies, otherwise complete 1 survey per site #):
   ASCEND-D: ______
   ASCEND-ND: ______
   ASCEND-ID: ______

5. Name of PPD/LDO person completing questionnaire: ________

6. Role of person completing questionnaire:
   a. RSM-L
   b. CRA
   c. LDO staff
   d. Other: ________

7. Check this box if site personnel was not available to complete questionnaire □
   Reason:
   a. No answer after 3 attempts [please ensure at least 2 attempts with SC + 1 with PI are documented in CTMS. If only PI was reached, no need to go through the entire survey, just check status of the site and who should be contacted for additional information. If no successful attempt, try again in 2 weeks.
   b. No time to provide answers to the Survey, but subject care is being maintained.
   c. Other - Describe: ________

Site level activities
8. Is research site opened/ temporarily closed/opened part time? (note: only select “temporarily closed” if ALL activities have stopped at the site – even remote activities)
   a. Opened normal hours
   b. Fully closed
   c. Opened part time
      a. If part time what days/hours? ______

9. Who (PI/SI/SC) from ASCEND research site staff is available to oversee the study(ies)?
For the first survey completed for each site, please complete the fields for the PI/SC/Sub-I/Other as applicable. For the subsequent surveys, only complete if there were changes from previously completed Surveys:

i. No changes from previously completed surveys (no need to re-enter name/role/email/phone)

ii. Changes from previously completed surveys (please update name/role/email/phone below)
   i. No (if no, no need to re-enter name/role/email/phone)
   ii. Yes (if yes, please update name/role/email/phone below)

PI
a. Name: _____
b. Email: _____
c. Phone: _____
d. Are the staff listed above available full time/part time?
   i. Full time
   ii. Part time
      If part time, what days/hours? ______

e. Check this box if this person is the primary contact for PPD □

SC
a. Name: _____
b. Email: _____
c. Phone: _____
d. Are the staff listed above available full time/part time?
   i. Full time
   ii. Part time
      If part time, what days/hours? ______

e. Check this box if this person is the primary contact for PPD □

Sub-I
a. Name: _____
b. Email: _____
c. Phone: _____
d. Are the staff listed above available full time/part time?
   i. Full time
   ii. Part time
      If part time, what days/hours? ______

e. Check this box if this person is the primary contact for PPD □

Other
a. Name: _____
b. Role: _____
c. Email: _____
d. Phone: _____
e. Are the staff listed above available full time/part time?
   i. Full time
   ii. Part time
If part time, what days/hours? ______

f. Check this box if this person is the primary contact for PPD □

As per COVID-19 Letter Pack that was distributed 31 March, PPD will be aiming to contact each site every 2 weeks during the pandemic.

10. Confirm with site staff what is a good day/time to set up the first call in 2 weeks? ________________

Subject study visits and potential safety (tick all applicable options)

11. Are site staff able to complete patient visits in clinic as per protocol at research site?
   a. Yes - If yes, are these full study visits or limited to a subset of procedures (e.g., checking HemoCue Hgb)
      i. Full study visits
      ii. Limited to a subset of procedures (e.g., checking HemoCue Hgb)
   b. No - If no, is a remote visit being completed:
      i. By phone or by telehealth (telemedicine)
      ii. At subject home
      iii. No remote visit is being completed (please add details to the Comments free text field below)

C. Is hemoglobin being checked:
   i. HemoCue (site/subject’s home)
   ii. Local lab
   iii. Not at all

12. Answer ONLY if site has subjects in ASCEND-D study (807), or ASCEND-ID study (410), or subjects in ASCEND-ND study (808) who transitioned to dialysis:
Are study subjects being dialyzed at their regular units? [reminder: ask site to provide information on a subject basis. In CTMS, Subject Screen, under the “Comments” free text field, enter #COVIDDIFFDIALYSIS to track subjects who have NOT been dialyzed at their regular dialysis units]
   a. N/A site does not have any subjects in dialysis
   b. Yes
   c. No [reminder: ask site to provide information on a subject basis. In CTMS, Subject Screen, under the “Comments” free text field, enter #DIFFDIALYSIS to track subjects who have NOT been dialyzed at their regular dialysis units]
   d. A combination of above

   ONLY answer next 4 questions if you answered ‘NO’ or ‘A COMBINATION OF ABOVE’ to last question and subjects ARE at new dialysis units
   i. Are the study staff (PI/SC) still able to have oversight of subjects dialysis? [reminder: ask site to provide information on a subject basis. If study staff will NOT have oversight of subject at the different dialysis facility to ensure no repeated double ESA dosing, subjects should temporarily stop RT and initiate SOC. In CTMS, Subject Screen, under the “Comments” free text field,
enter #COVIDSOC to track subjects switched to temporary SoC OR #COVIDNOTRT to track subjects with NO anemia treatment (ie. switched off RT and SoC not an option)
   a. Yes
   b. No [reminder: ask site to provide information on a subject basis. If study staff will NOT have oversight of subject at the different dialysis facility to ensure no repeated double ESA dosing, subjects should temporarily stop RT and initiate SOC. In CTMS, Subject Screen, under the “Comments” free text field, enter #COVIDSOC to track subjects switched to temporary SoC OR #COVIDNOTRT to track subjects with NO anemia treatment (ie. switched off RT and SoC not an option)]
   c. A combination of above

ii. Are the staff at the new units aware that the patients are participating in the ASCEND study?
   a. Yes
   b. No
   c. A combination of above

iii. Are the staff having difficulty obtaining information about the subjects including AE/SAE?
   a. Yes
   b. No
   c. A combination of above

iv. Are subjects able to continue randomized treatment? (Select all options that apply) Jagadeeswari, can we allow them to select all options for this question?
   a. No - If subjects cannot continue randomized treatment is there a possibility that subjects will resume randomized treatment when the subjects return to their regular dialysis units?
      i. Yes
      ii. No
   b. Yes - If subjects can continue randomized treatment at the new unit, what process has been implemented to prevent double dosing - Add Comments:

Monitoring Activities / Data Queries

13. Are the site staff able to complete onsite AND remote monitoring visits as planned?
   a. Yes
   b. No - If no, can monitoring visit be done remotely?
      i. Yes
      ii. No
14. Are the site staff able to process data queries during COVID-19 pandemic?
   a. Yes
   b. No
   c. Limited

Shipments
15. Is the research office/dialysis centre able to accept randomized treatment supply shipments as normal?
   a. Yes
   b. No - If no, is there an alternative address to send shipments?
      i. No
      ii. Yes, list: _______________

16. How often is the site monitoring randomized treatment storage temperature?
   a. Normal RT temperature monitoring on business days
   b. Partial RT temperature monitoring – describe: _______________
   c. No RT temperature monitoring is possible

17. Is the site able to ship lab samples to Q2 central labs?
   a. Yes - If yes, are there any restrictions on days/couriers?
      a. No, no shipment restrictions
      b. Yes, specify _______________
   b. No - If no, does the site have capacity to store frozen samples?
      a. Yes
      b. No

18. Does the site have sufficient lab kit supplies?
   a. Yes
   b. No - If no, has this issue already been flagged to PPD?
      i. Yes
      ii. No

Comments (please feel free to add any additional information about the site status or clarify any responses provided): _______________