Supplemental Materials

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

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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

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, 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

1. 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.

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 <u>ONLY</u> 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? **[<u>reminder</u>: ask site to provide information on a subject basis. In CTMS, Subject Screen, under the "Comments" free text field, enter <u>#COVIDDIFFDIALYSIS</u> 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 **[<u>reminder</u>: 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): _____