

GlaxoSmithKline plc
Investor Science Event
Getting ahead of anaemia due to chronic kidney disease
ASN Kidney Week 2021
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Mick Readey: Good afternoon and good evening, welcome to GSK's Investor Science Event: Getting ahead of anaemia from chronic kidney disease, for investors and analysts from the American Society of Nephrology Kidney Week 2021. I'm Mick Readey, your moderator for today's call and a member of the GSK IR team; we are here today for an update on daprodustat, a potential best-in-class new medicine for the treatment of anaemia of chronic kidney disease. As usual, the presentation materials are available on gsk.com and were sent to our distribution list earlier today. Please also note that the data presented on today's call are available on the ASN website or in the accompanying publication on the *New England Journal of Medicine*.

Before we get started, I would like to thank Frannie DeFranco from the IR team for her contribution to today's call.

Cautionary statement regarding forward-looking statements

Now, a quick reminder of the usual safe harbour statement and forward-looking statements disclaimer.

Speakers

We are joined on the call by Dr Hal Barron, Chief Scientific Officer and President of R&D, and Luke Miels, Chief Commercial officer at GSK. We're also pleased to welcome Dr Ajay Singh, Senior Associate Dean for Postgraduate Medical Education from Harvard Medical School, and Principal Investigator for daprodustat's ASCEND Phase III Programme, including the ASCEND-D and ASCEND-ND Phase III data, that were presented as late-breaking abstracts at ASN on Friday.

Agenda

This is today's agenda. I anticipate the call will last around one hour, with half for presentation and the remainder for Q&A. Naturally, we will try and ensure we take as many questions as possible. For the Q&A portion of the call, we will be joined by John Lepore, SVP Research, and Chris Corsico, SVP Development. As a reminder, questions can be asked via telephone by using *1. Before I hand over to today's presenters, I'd like to remind

you that the call is being recorded and that a replay will be available after the event. And with that, I will now hand over to Hal.

Daprodustat: a potential best-in-class treatment
Dr Hal Barron
Chief Scientific Officer and President, R&D

Thank you Mick, and a warm welcome to everyone on today's call.

Daprodustat: a potential best-in-class treatment for patients with anaemia due to CKD

Let me start by saying how pleased I am with the positive Phase III results from the daprodustat ASCEND programme that were presented on Friday. Daprodustat is a drug that acts as a HIF prolyl hydroxylase inhibitor, a target we chose to pursue because the genetics strongly suggest a role in stimulating erythropoiesis, as well as compelling world-class biology that actually led to a Nobel Prize. Daprodustat's success in Phase III lends further credibility to our R&D strategy, which focuses on human genetics and functional genomics, to identify targets with a higher probability of success.

Our robust clinical development programme recruited more than 8000 patients in well-designed studies with active controls, and resulted in very consistent clinical findings in both efficacy and safety. This positions daprodustat as a potentially best-in-class oral agent for anaemia due to chronic kidney disease.

We are also quite proud that the ASCEND programme reflected real world management of patients with chronic kidney disease, and specifically included both dialysis and non-dialysis dependent patients in separate well-powered studies aligned with requests from regulators.

Lastly, we are inspired by what this potentially transformative medicine could mean for patients. There are more than 700 million people worldwide living with chronic kidney disease, and one in seven of them suffers from anaemia. The current standard of care for these patients is an erythropoiesis stimulating agent, or an ESA, administered via subcutaneous injection or as part of dialysis.

Although these can provide benefits to patients, only around 30% of non-dialysis patients today receive ESA treatment, due to the administration challenges. With daprodustat we believe we have a convenient and flexible oral treatment option for both dialysis and non-dialysis patients, which has shown improvements in quality of life, and predictable increases in haemoglobin.

With that, it's my pleasure to hand over to Dr Singh, to discuss the results of the studies presented at ASN on Friday. Dr Singh.

ASCEND Phase III Programme

**Dr Ajay Singh
Senior Associate Dean
Post graduate Medical Education, Harvard Medical School
and Principal Investigator**

Thank you very much, Dr Barron. Before I get into the next slide, let me just say thank you everyone for joining. I know it's Sunday and there are many better things you probably have to do, but I really appreciate the time you're giving.

I think it's important to give you a little bit of background about myself before I talk through the slides. I've been practising nephrology for the past 35 years, both in the UK and the United States, and have been involved in anaemia studies for the past 20 years. Fifteen years ago, I published the CHOIR study in the *New England Journal of Medicine* and testified to the House Ways and Means Committee of the US Congress, and spoke about the limitations of current therapies.

A few years later, we published the TREAT study, a placebo-controlled trial, again reinforcing the limitations of therapy. So, it's really exciting for me at a personal level to share with you this data because I think we are meeting an unmet need that currently exists in the treatment of anaemia among kidney-disease patients, not only because current therapies have raised issues around safety, including cardiovascular safety and tumour-related issues, but also the fact that we haven't, in any trials, been able to effectively demonstrate that there is an improvement in quality of life.

This trial programme I am particularly proud of because I think it could be an important step in the right direction for our patients with kidney disease, particularly those with chronic kidney disease who are not receiving therapy as Dr Barron spoke about.

ASCEND Clinical Trial Program

In this slide, what you see is an overview of the ASCEND clinical trial programme. It included five Phase III clinical trials, and more than 8000 patients. There was a target to investigate the efficacy and safety of daprodustat across a spectrum of patients with chronic kidney disease, or CKD.

The CVOT trials that you see at the top include clinical trials labelled ASCEND-D in dialysis, and ASCEND-ND in non-dialysis, provides approximately 6800 patients and

approximately 14,200 patient years of experience, so a tremendous amount of experience over the way we are presenting today.

My presentation will focus on the two cardiovascular outcome trials, the dialysis and non-dialysis population, although I will share with you programme-level cardiovascular safety at the end of the presentation.

ASCEND-D and -ND: Trial Design

This next slide shows you the overall structure of the ASCEND-D and -ND trials. Both trials were event-driven, open label, randomised, active-controlled, parallel-group, multicentre Phase III trials, conducted in 41 countries worldwide.

Both trials included, as you can see on this slide, a four-week screening period and then a four-week run-in period before randomisation marked by the letter 'R', in patients who were randomised, one-to-one, either to daprodustat, oral administered daily, or to an ESA comparator.

Now, if you see this box, you see ESA (D) and darbepoetin SC (ND). Let me explain that to you. For ASCEND-D, epoetin alfa was administered to haemodialysis patients and darbepoetin alfa to peritoneal dialysis patients. That is because peritoneal dialysis patients are home patients and they needed a subcutaneous injection, and that is why darbepoetin was used instead of epoetin alfa.

For the -ND study, ASCEND-ND study, darbepoetin alfa was the active comparator. For both trials and for both arms, the drug was dosed to a haemoglobin target of 10-11g/dL. Now remember, in healthy people who are not on dialysis or with kidney disease, the normal haemoglobin is around 13-15g/dL, but the target of 10-11g/dL was something that was decided in conjunction with the regulators, both in the United States and in Europe.

Now the same iron management protocol was applied to both arms, and you see that in the box right in the middle.

With respect to the co-primary endpoints, as shown on the righthand side of the slide, these were two. One was the mean change in haemoglobin from baseline to the average during the primary evaluation period. That represented Week 28 through Week 52. The second co-primary endpoint was time to Major Adverse Cardiovascular Event or MACE. As you know, MACE is defined as all-cause mortality, non-fatal myocardial infarction or non-fatal stroke.

Again, these were events-driven trials where the trial ended when the target number of MACE events reached 664. The key entry criteria are highlighted on this slide as well. Details of these entry criteria were included in the published manuscript that became

available to everyone – I'm sure you've received it; they were published in the *New England Journal of Medicine*.

I'm not going to go into the details of them, but you can see the key criteria and of course you can look at them in more detail in the papers.

Patient Disposition

This slide discusses the patient disposition. The first most important point here is that we used an intention-to-treat analysis to look at the ITT population. The key points here with respect to patient disposition were that few patients withdrew and the withdrawal rates were similar across treatment groups. A premature discontinuation randomised treatment was balanced across treatment groups, and the known vital status was high in both trials across both treatment groups.

Why is all this important? Because it really speaks to the high internal validity of the trials. It is very important to know what happened to the patients and whether whatever happened to the patients with respect to withdrawal was balanced between the two arms. I think this is something I have a lot of pride around because I think the conduct of trials is a very important part of doing trials.

The next thing you see is the number of randomised patients. We had 2964 patients randomised in the dialysis study, and 3872 patients randomised in the non-dialysis study. You can see, when you look at this with intention-to-treat, the numbers in both arms.

Co-primary Efficacy Endpoint: ASCEND-D

Here you can see the co-primary endpoints. Before I speak to that, I want to add one little piece of information. In the papers you will see baseline data on the two patient populations, the samples that were recruited in the study, the D study and the ND study. Baseline data or Table 1s, as we traditionally call them, are really important to look at because the Table 1s in both studies show that there was balance again on baseline characteristics between the two trials.

That's really important for two reasons. One, it shows that the results reflect randomisation having worked, because if you randomise properly, you would expect there to be a balance between the two arms, against speaking to internal validity. The second reason it is important to know about the baseline data. You want to know whether these patients reflect what we generally see in clinical practice. Are these results generalisable to clinical practice, and in both these cases, the answer was that they were. Again, I refer you to the papers in the journals for more information about them.

Co-primary Efficacy Endpoint: ASCEND-D

This next slide looks at co-primary efficacy endpoint for haemoglobin, and remember, this is defined as the mean haemoglobin change from baseline to the evaluation period for Weeks 28-52. In general we are looking in the pre-specified way the intention-to-treat population.

We are first looking at the ASCEND-D data. In the blue panel, you see the message from this. Daprodustat was noninferior to ESA for the mean change in haemoglobin from baseline to the evaluation period, i.e. from Weeks 28-52, shown in the shaded area for the graph just below it.

It is important to know that in the ASCEND-D trial for the co-primary haemoglobin endpoint, the adjusted mean treatment difference was 0.08g/dL, with a 95% confidence interval of 0.12-0.24g/dL. The noninferiority margin, which is again pre-specified and agreed upon with the regulators, the noninferiority conclusion was supported here because the confidence interval for the treatment difference is entirely above the pre-specified -0.75g/dL that represents that noninferiority margin.

What you also see on the slide, the mean haemoglobin profile during the trial for dapro in purple and for ESA control in orange. You can see that the mean haemoglobin for both treatment groups remains in the analysis haemoglobin range of 10-11.5g/dL. This was the case for the ESA hypo-responder sub-group as well, supporting the notion that dapro works, and works effectively, and that our protocol worked and the protocol worked well in terms of determining the dosing of dapro. But the second is that dapro worked well in patients who were ESA or ESA hypo-responders.

Co-primary Efficacy Endpoint: ASCEND-ND

If we turn to Slide 12, we can see the co-primary efficacy endpoint for haemoglobin for the ASCEND-ND trial. Here, similar to the previous data, dapro was also noninferior to darbepoetin alfa for that same co-primary haemoglobin endpoint.

The mean adjusted treatment difference was 0.08 – you can see that in the box on the righthand side -, with a confidence interval of 0.03-0.13g/dL, which is entirely above the pre-specified -0.75g/dL for the noninferiority margin, so it met the criteria for noninferiority.

Now the corresponding graph on the slide here, the left hand side, displays the mean haemoglobin profile during the trial for dapro which is marked in purple, and darbepoetin in orange, and you can hardly see any difference, and we superimposed them over each other specially during that shaded evaluation period.

In this trial as well, the mean haemoglobin for both treatment groups remained in the analysis haemoglobin range of 10-11.5g/dL, and again, for both the D and ND trial, with

respect to noninferiority, we met the noninferiority criteria for this, so the trials were successful with this co-primary endpoint.

First Occurrence of Adjudicated MACE

Slide 13 looks at the first occurrence of adjudicated MACE. Let me spend a second on this. Adjudicated MACE, 'adjudicated' meaning that these were events that were adjudicated independently by Duke Clinical Research Institute that were the endpoints committee, the Clinical Endpoints Committee, for this trial.

MACE, as you recall, is mortality, non-fatal myocardial infarction and non-fatal stroke. These analyses are all pre-specified in our statistical analytical plan, and our analyses that are based on the ITT population, based on obviously agreement with the regulators.

Let's have a look at the results here. On the left are the results for the ASCEND-D trial where 25.2% of dapro patients and 26.7% of ESA-controlled patients experienced a MACE event. Dapro was noninferior to ESA with a hazard ratio of 0.93 and a 95% confidence interval of 0.81 to 1.07, and we'll discuss why in a second, but let me just hold that thought with you. I shared with you the hazard and the confidence intervals.

On the right are the results for the ASCEND-ND trial where 19.5% of dapro patients and 19.2% of darbepoetin patients experienced a MACE event in the trial. Here again, dapro was also noninferior to darbe with a hazard ratio of 1.03 and a 95% confidence interval of 0.89 to 1.19.

Now for both these MACE endpoints, for both the trials, the noninferiority conclusions are supported because the confidence interval for the hazard ratio is entirely below the pre-specified noninferiority margin of 1.25.

Also on this slide, you are all familiar with Kaplan-Meier curves, and so you see two Kaplan-Meier plots, one on the left for the D trial, and on the right for the ND trial. These show the percent of patients with a MACE event over time. Dapro is shown in purple and ESA control is shown in orange. As you can see, the lines are not only very close together, they are essentially superimposable on each other, so it is not at all surprising that the noninferiority criteria were met.

In the boxes in the middle you see the components of the first occurrence of adjudicated MACE. Again, the details of all of this are laid out in much more detail in the papers that were published on Friday, but let me just walk you through them.

On the left you see first occurrence of adjudicated MACE with dapro and ESA for the D trial, and very similar when you look at the components that are all-cause mortality,

myocardial infarction or stroke. Then on the righthand side you see the ND data which, again, depicted in a similar fashion, show the similarity between both dapro and darbe.

So, again the message here for this important co-primary endpoint was that noninferiority was achieved because the upper boundary of the 95% confidence interval for HR was lower than the pre-specified NI margin of 1.25.

MACE Supplementary Analyses

On this slide we are looking at the MACE supplementary analyses, and of course, as you know, this is always done in much greater detail and discussed in the papers, but I'm going to share with you some key messages.

What you see here are the analyses conducted on the co-primary MACE endpoint, and, as you know, the results of the primary analysis was ITT, which was a pre-specified analysis, and this included both on and off treatment MACE events. This is shown on the first row for both, so you see on the left the ASCEND-D, and on the right the ASCEND-ND, and the first row is first occurrence of MACE, the primary analysis.

You can see here that it's almost close to 1 in this case with respect to dapro versus ESA for both, so the noninferiority criteria were met here.

Next, an on-treatment analysis was run, and this excluded MACE events if they occurred more than 28 days after the patient's last dose of treatment. You can see that on the left, very similar to the primary analysis; on the right, it's an outlier for first occurrence of MACE on-treatment.

I think it's important to emphasise the reason for this is that we're looking at this as an on-treatment analysis, and as you and I know through all these years, essentially an on-treatment analysis is not the same as the pre-specified ITT analysis, and the pre-specified ITT analysis is essentially what you do as a clinical triallist, whereas the on-treatment analysis is essentially opening up the dataset after the trial has essentially been done, and the analysis is open to a variety of confounding factors as well as treatment biases. In this case, post hoc analysis demonstrated that the differential dosing of dapro compared to darbepoetin explained in large part this outlier effect, and the effect attenuated once you took the differential dosing frequency into account.

The next two rows show further ITT analysis which included both on and off-treatment MACE that were run. On the left you see the analysis that excluded MACE-related to COVID-19, and also MACE that occurred after the target 664th first events were reached in the dialysis trial. Again, very similar to the primary analysis.

On the right, in the ND trial, an additional pre-specified ITT analysis was run that included additional covariance in the analysis model. Again, you see it is very similar to the primary ITT analysis.

I think that it's important to know that this is discussed in much more detail in the papers that were published.

Principal Secondary Endpoints

Slide 15 looks at the principal secondary endpoints. The message here is that they did not meet multiplicity-adjusted statistical significance for superiority, using the Holm-Bonferroni method.

On the left, you see the data for the ASCEND-D trial; on the right, you see the data for the ASCEND-ND trial for these principal secondary endpoints.

The first three principal secondary endpoints were consistent between trials and included the superiority analyses of time to first adjudicated MACE, which have been assessed for noninferiority in the primary analyses, as well as superiority assessments for the adjudicated MACE+thromboembolic events and adjudicated MACE+hospitalisation events for heart failure endpoints.

It is important for one thing which I think stands out. It is that the MACE+thromboembolism events is 0.88, with a 95% hazard ratio of 0.78 to 1.00. MACE+thromboembolism favours dapro in terms of fewer MACE+thromboembolism events, with dapro as compared to darbe. When you look at the Kaplan-Meier curves, and you can look at that in the paper, the D paper which is published, you see that the Kaplan-Meier curves diverge in favour of dapro pretty early on after randomisation occurs, and they continue to gradually diverge.

When you look at the thromboembolic events separate from MACE, there are a higher number of thromboembolic events amongst patients randomised to darbe compared to those randomised to dapro, so with respect to thromboembolism, a lower number of events for dapro patients.

What seems to be driving this are vascular access thromboembolic events, and you can see that in the paper itself, and I would encourage you to look at that data.

When you look at the ND, there was no difference. They were very similar between both the dapro and the darbe.

Now, when you look at the ASCEND-D trial with respect on the on-treatment average monthly IV iron dose, which is shown on the bottom left, that is the on-treatment average

monthly iron dose in milligrams from baseline to Week 52, we saw a benefit in iron parameters consistent with the Phase II findings, so there was a benefit in iron parameters. This included a lower level of hepcidin. As you know, hepcidin is a very powerful regulator of iron within the body and regulates iron egress out of the enterocyte, out of the small intestine into the body, and lower levels are better in terms of allowing for more absorption of iron. So the level of hepcidin was lower in patients randomised to dapro, there was also a higher level of TIDC in patients randomised to dapro.

However, we did not see a significant treatment difference in iron utilisation, although IV iron use was reduced in both treatment groups. It was a little bit lower, -9.1, wide confidence intervals, probably not clinically meaningful. We don't have to look into this in much more detail because there were a number of things that were going on. There was an iron management protocol, most patients on dialysis receive iron intravenously, they don't receive it orally. Most of our patients did too, and there may not have been an opportunity to actually enhance oral iron absorption because these patients weren't receiving oral iron, and one can speculate that it might explain why you see also a benefit in iron parameters, but no difference in iron utilisation.

On the righthand side, you see the other principal secondary endpoint, and that is for CKD progression in the ND trial. CKD progression, as you can see on the slide, is defined as a 40% decline in eGFR, or progression to ESRD. These definitions are now widely accepted and widely accepted by the regulators. The hazard ratio was 0.98 with confidence interval 0.84 to 1.13, so no difference with respect to CKD progression in the ND trial.

Adverse Events

We are now looking at adverse events, and we are looking at adverse events in the safety population. The safety population are defined as randomised patients who received at least one dose of drug. We are reporting here treatment-emergent events. Additional information on adverse events is contained in the primary management for both trials that have been published, so I'm only going to go over this in a summary fashion.

In general, rates of treatment-emergent adverse events and serious adverse events were similar between treatment groups in both trials. Rates of pre-defined treatment-emergent adverse events of special interest were also generally similar between the treatment groups in both trials. Two of the adverse events of special interest, oesophageal and gastric erosions and cancer events, actually displayed conflicting results between the trials, and this is undergoing further investigation.

Post hoc analysis that is described in the management for the primary ND trial, which explored the impact of the differential dosing frequency on the treatment-emergent results,

and these analyses demonstrated an attenuation of the imbalance for cancer events, but not for gastric/oesophageal erosions.

The other point is that these are, again, on-treatment analyses, and as you know, what's important to patients is really what happens in the ITT approach, when you randomise this drug and you see events or versus, on the right, the comparator, and you see the results. When you compare it based on ITT, in fact there is no difference, there is balance between the two. I think for cancer, these results, the post hoc analysis plus looking at this with ITT, is very reassuring.

ASCEND Program-Level Cardiovascular Safety Data

Slide 18 is about pulling the lens back and looking at a central level cardiovascular data. We are looking at the data for cardiovascular events that were adjudicated in all of the five Phase III trials, although it's important to note that the three smaller trials were not designed for MACE evaluation. The two, the ASCEND-ND and D, the results of which I have already described, were designed and powered to look at MACE, whereas ID, instant dialysis, PD, which is three-times-a-week dialysis and NHQ, were not designed for that.

What I'm showing you here are the four trials at the top, and just summarising the MACE results reached for the ASCEND-NHQ, that is the trial that focused on the quality of life, because that trial was even more different than the others in that it was of very short duration, only 28 weeks.

Even so, focusing on NHQ for a second, MACE events, 4.9% in dapro and 6.2% in placebo, the NHQ trial was a randomised-controlled, double-blind, placebo-controlled trial and that's why placebo is used. The results of the NHQ trial were presented as an oral communication on Friday afternoon at the American Society of Nephrology meeting.

Anyway, that's the NHQ. Let's go back to the data above that. What you see here on this slide is the first forest plot, and you will see the MACE results by treatment group expressed as a rate for 100 patient years for the four active control trials, and you can see that there.

The second forest plot on the right hand side contains the absolute rate difference per 100 patient years between the treatment groups. You can see that the MACE profiles were generally consistent across treatment groups in all of the trials. This is really important. Now we are looking at even more patients and even more patient years of experience, and really the results are very consistent with respect to MACE, not only with respect to ND and D, but also across the programme as a whole.

ASCEND Program-Level Cardiovascular Safety Data

If you go to Slide 18, we are looking at the ASCEND Program-Level Cardiovascular data with respect to MACE components. Remember, MACE is mortality, non-fatal MI, non-fatal stroke. What you see here is that the component events that make up MACE show consistency across the board with respect to all the trials and across the treatment groups, dapro versus comparator ESA. This again reinforces that not only in the individual two cardiovascular outcome trials, but also across the programme, the MACE profiles are very much consistent, and this I think is really important.

Summary and Conclusions

The last slide is the summary and conclusions. Here, the important points are that dapro was as effective as conventional ESA therapy in treatment anaemia of CKD.

Dapro was noninferior to ESA with respect to cardiovascular safety and no new safety signals were observed.

Looking forward, I believe, and I think my nephrology community, speaking for them having done this for many, many years, can confidently say that dapro could represent an oral alternative to ESA for treating anaemia of CKD in both dialysis and non-dialysis patients. I think it presents an opportunity, particularly so in non-dialysis patients for example, as Dr Barron, pointed out, who hitherto have essentially been under-treated. I think that's a great opportunity.

I think it also represents an opportunity in dialysis patients and non-dialysis patients because it might target two arms of the anaemia-treatment paradigm, not only ESA deficiency because kidneys become diseased and so you need erythropoietin, but also iron.

We still have to do many more studies in iron, but I think the benefit on iron parameters is really very intriguing, and will need to be looked at in more detail.

I just want to say thank you again for your attention, and I'll turn it over to Luke Miels.

Commercial opportunity
Luke Miels
Chief Commercial Officer

The prevalence of anaemia increases as CKD progresses; it is associated with an increased risk of hospitalisation, cardiovascular complications and death

Firstly, on this slide you can see that CKD is a significant global burden, and as Hal mentioned, there are more than 700 million people worldwide living with CKD.

Patients in the more advanced stages of 3 to 5 are the target group for daprodustat, and we know that this patient group is under-diagnosed, under-treated, or not treated to target levels.

It's also important to note that this is a progressive disease which requires many years of treatment and increasing levels of specialty care. The increasing burden for patients underlies the need for an effective, safe and convenient treatment, and these patients usually have other comorbid conditions like diabetes and TB disease, further complicating therapy choice and management.

Currently, patients are treated with iron supplements and regular injections of an ESA, which brings administration challenges.

HIF-PHI class could become the new standard of care

With the positive Phase III data that you have just heard about today from Dr Singh, we believe there is a significant opportunity to provide a differentiated medicine in an area of high unmet need.

In the non-dialysis population, there are more than 1.3 million people under treatment in the US and the EU, and only about 30% of this population are treated with an ESA.

Furthermore, around half of these patients discontinue their treatment within one year. Consequently, there is a major opportunity to impact the lives of patients in the non-dialysis setting, and we believe that daprodustat could potentially offer a new, convenient oral treatment option.

For the dialysis-dependent population, I want to specifically highlight two populations that we think daprodustat could immediately help – those already receiving dialysis at home and those who are on a high dose of ESA and require multiple injections, known as hypo-responders. Together these two sub-populations make up around a quarter – and growing – of the dialysis population.

Patients receiving dialysis at home account for around 12% of total dialysis patients under treatment, and this proportion is expected to grow to around 25% by 2025. These patients need cold storage and to inject their medicine, which brings administration challenges. An effective and convenient oral option has the potential to simplify their treatment regimen and improve their quality of life.

For the hypo-responders, these patients also represent around 12% of the dialysis population, but they bear a significant proportion of the costs, as they can receive up to six times the standard ESA dose. In this setting, daprodustat has the potential to be a

transformational medicine with simple oral dosing replacing the high and frequent injection burden and the costs.

Japan: *Duvroq* has achieved market-leading share

In collaboration with our partner, KKC, *Duvroq* was launched in Japan in August of 2020, nine months after the first HIF. The medicine has already surpassed the main competitor and is now the market leader with 47% class share.

One of the main drivers is our favourable label, which enables patients to switch directly from an ESA, a competitive advantage we intend to seek to replicate in our label in other markets. In Japan we are now seeing 75% of patients coming from switches and the other 25% coming from new patient starts.

We are also encouraged by the feedback we've received from nephrologists, which is driving the strong momentum and uptake in both the non-dialysis and dialysis-dependent populations.

The successful launch in Japan has provided us with lessons that will apply globally, including the importance of early treatment with external experts and healthcare providers. We've also seen positive trends in our target populations, and this supports our confidence in the differentiated benefits of this potential new medicine.

Daprodustat: an innovative, convenient oral treatment for patients with anaemia due to CKD

The strong clinical data from the ASCEND programme provides us with a set of strong messages that we can bring to physicians and patients, assuming of course that we can gain regulatory approvals, and these include, a convenient oral option for the non-dialysis and dialysis patients which may overcome their requirement for regular injections; with the ability to manage haemoglobin in a predictable manner and the potential for flexible dosing; and a demonstrated improvement in quality of life for patients.

With the benefit of these compelling messages, we see a significant opportunity to transform patients' lives and to drive commercial success for daprodustat.

We have previously highlighted a sales potential of £0.5-1 billion, and in this range we assumed daprodustat would be third to market.

Now, clearly the competitive situation has encouragingly moved in our favour, meaning there is certainly upside relative to our previous assumptions. We are now

sharpening our focus on preparations for forthcoming regulatory interactions, and we will keep you updated as we move through that process.

We have now made the decision that we will commercialise daprodustat alone, and since 2017 we have strengthened our marketing and medical capability in the Specialty area by hiring over 900 employees, and we have a strong base to build off in nephrology given the established leadership position of *Benlysta* in lupus nephritis.

In terms of the next steps, we plan regulatory submissions to the FDA and the EMA in the first half of 2022. We are excited to bring this potentially transformative medicine to market as soon as possible for the benefit of patients, so we will be doing everything we can to accelerate our filing timeline.

With that, I want to thank you for your time and I will pass it back to Hal to open up for Q&A.

Question & Answer Session

Graham Parry (Bank of America Merrill Lynch): Thanks for taking questions, and for taking the time to present the data to us this evening as well. The first question is just on FDA attitude to the endpoints you're using, so in the roxadustat briefing documents FDA stated that it's generally asked sponsors to show noninferiority on MACE, an active comparator in dialysis and placebo in non-dialysis, but the ASCEND-ND file was run against an ESA, which has a boxed warning for cardiovascular events, so how comfortable are you that placebo control isn't something the regulators are going to want to see, especially given that the hazard ratios are all trending slightly above 1, and the upper confidence intervals are pushing 1.2 range in the primary and key secondary endpoints?

Then secondly, you've highlighted a £3 billion addressable market opportunity there on ESA markets in the US and Europe, and your peak sales guide was £0.5-1 billion, are you assuming that you can expand the non-dialysis market, and let me say there's an upside to your £1.5 billion, can we assume the £0.5 is out of the picture and perhaps just give us some framework around where you think the 1 could go.

Then lastly, the editorial highlighted the excess cancer and GI erosion risks as problems, and also in the dialysis the thrombosis hazard ratio was 1.81, although that wasn't statistically significant. Given your comments on the Q3 call around commercial opportunity being linked to how the editorial treated the data, what are your thoughts now on that editorial, and how that might impact your commercial opportunity? Thanks.

Hal Barron: Thanks, Graham, a lot of questions there. Maybe what we could do, Luke, if you want to take firstly the commercial question, and then Dr Singh, maybe I could ask you to comment on the safety and thromboembolic events that were highlighted by Graham; then to the extent that you could also comment on the trial design of the non-dialysis having an active comparator, and at the end I can make a comment on the regulatory component.

Luke, do you want to start with the commercial question?

Luke Miels: I think on the editorial overall I'll leave it to Dr Singh and Hal to comment further, but I think it was relatively balanced, clearly a lot of mentions of vadadustat which probably reflects the background of the contributor, the author. I think it's probably worth expanding in the Q&A the intention to treat versus on-treatment, particularly in terms of the comments made around cancer, but I'll leave that for the other speakers.

I think in terms of the forecast, I'll give you an update today, but the key assumption is that it was third to market, that's now clearly changed. At a macro level, the way I look at this is, when you look at differentiation versus options available in terms of epo, you have relative simplicity with dapro. I think in the non-dialysis population of course, it's oral versus injection or infusion, there's no cold chain and again - this is subject to regulators – we don't expect restrictions on complement oral iron or phosphate binders, no expected DDI with statins, and again, I think you have this higher morbidity in complex conditions with CPD and Type 2 diabetes.

I think the other thing is – which we can supply you the papers behind the data that we've quoted – you have a large proportion of stage 3 to 4 patients being managed by primary care physicians in the US, and that, even in a nephrology setting, these are relatively undertreated patients who have anaemia are being undertreated. In dialysis and in home dialysis, clearly when we talk to the dialysis providers they're trying to increase the level of home dialysis, and I mentioned the hypo-responders can also be managed. It's interesting, they're around 10-12% of patients and around 40% of the costs, which obviously has consequences when you look at the bundle.

So net/net, I think it's fair to say probably two-thirds of the volume will be in the non-dialysis setting, again subject to the final label that we see.

Hal Barron: Thanks Luke. Dr Singh, do you want to comment on the safety profile that Graham brought up, and then I will conclude with some of the regulatory component.

Ajay Singh: I think the two points are, first, with respect to thromboembolism, there were some disparate results between the D and the ND trial. The D trial showed essentially that there were a higher number of thromboembolic events in patients that were treated with darbe versus those treated with dapro with the dialysis patients, and that was mostly being driven by the number of vascular access thrombosis events. With dialysis, as you know, vascular access thrombosis is much more common because the access has been used, and there's a higher - not hugely higher, but somewhat higher – prevalence of grafts, because these grafts are placed in and around the time these patients are started on dialysis.

In the ND trial I think as you cited, there were a numerically higher number of thromboembolic events, non-fatal events, in the patients who were randomised to dapro, and slightly less so in darbe. For the journal, the reviewers, the nephrology community as a whole I think, this wasn't particularly a problematic thing. I think these are very complex patients, both dialysis and non-dialysis patients, neither of those results reached statistical significance. Particularly with respect to when you're looking at the way you analyse the data, doing an analysis with a co-primary which didn't show statistically different results from now, I think it's very important not to over-interpret any of the analyses of any of the components or any of the principle secondary endpoints. That's number one.

I think with respect to you raising the issue around cancer in the ND trial, honestly I'm not exercised by it at all, because firstly, the total number of events was relatively small. Secondly, it was conflicting between the two trials, like with the thromboembolism between the D and the ND, and the D, cancer rates favoured dapro a little bit as compared to darbe, whereas in the ND it favoured darbe as compared to dapro. Remember that these are not intention-to-treat analyses. In the intention-to-treat analysis, what you do is trial it and that is the important information to bear in mind.

If you go into the presentation and to the slides, I think there are some back-up slides that perhaps Mick can show - he's showing them right now, I can see them – you see that, the treatment of emergent definitions which are defined using the on-treatment approach, and then on the right hand side you see ITT definition, which is all patients really care about, and you see that there's really no difference.

So I'm not exercised about this at all, and nor were the reviewers, nor were the editors, nor were the people who listened in on the presentation and wrote comments and questions at the ASN. I hope that answers the question.

I can't speak to the regulatory stuff; I'm going to turn that back over to Hal.

Hal Barron: Thank you, Dr Singh. Let me just highlight the intent-to-treat definition. Remember, intent-to-treat is when a patient gets randomised to one arm versus the other, and then you follow up for the entire study period and you can see, I think quite clearly, the difference in cancer rates on the right side of this slide are almost identical, and this is of course the primary endpoint, the way trials should be examined. I just want to put an exclamation mark on that, because the 1.03 really I think highlights the key here that there is no difference.

Let me just comment on your question about the active control in the non-dialysis. I think it's important to remember that many patients, as we highlighted, who have anaemia from chronic disease but are not in the dialysis setting, have significant symptoms from their anaemia and would be candidates for epo, but because of the need for subcutaneous administration many of them do not get any ESAs, and it's those patients that we think really would benefit from dapro, and therefore the design is as such.

I should also highlight that, while we don't comment on any specific conversations we've had with regulators, I'd like to reiterate that the design of both studies, the sample size, the analyses, particularly the primary endpoints of intent-to-treat, confidence intervals, etc., were all done in strong collaboration with the regulators, so we're very confident both in the data and the design.

Ajay Singh: Let me just add something, Hal, for a second. I was involved in the CHOIR trial, where we had an active comparator, as well as being involved on the Executive Committee of the TREAT trial where we tried to do a placebo control trial. It is important to know that in the TREAT trial, we had an enormous difficulty in getting that trial done. I think the general feeling is that the standard of care, if you actually want to randomise patients to treatment, is to treat them in the control arm with ESA. I think it's an important point, and we had a lot of difficulty, and I think that's why the regulators essentially asked you guys to design trials which had an active comparator.

Hal Barron: Thank you for that extra point. Okay, let's get to the next question.

Laura Sutcliffe (UBS): Hello, thank you. The first question is on your dialysis trial. I think if I look at the equivalent vadadustat trial there are a greater proportion of patients in your trial having events in both arms, so could you perhaps just talk to the aggregate risk profile of the patients in your trial, and whether you think they look like normal" dialysis patients?

The second question is on the commercial strategy in dialysis. Just in the market where it is quite possible that a large chunk of it could be off limits, if daprodustat is approved, does your success depend on you getting non-dialysis on the label, or is that the wrong way to think about it?

Then, finally, just on the hypo responders, please. If I remember correctly, the FDA took quite a dim view of how this was presented in the roxa package. I think they said there was no specific evidence supplied, or something like that, so could you just maybe talk about how you plan to get around that problem? Do you have enough there that would be classed as specific evidence in the hypo-responder population? Thanks.

Hal Barron: Thanks, Laura. Dr Singh, maybe you could take the baseline covariant differences question from Laura, as well as maybe briefly comment on the hypo responders, and then we will turn it over to Luke for his thoughts on the commercial strategy and non-dialysis.

Ajay Singh: Yes, so I think the simple answer to your question is, are they the typical sort of patients we take care of on dialysis, and the answer is yes, but let me be a little bit more specific.

We had a good representation, I think an appropriate representation, of people who are African Americans. As you know, in the US there is a significant number of patients who are African American, and, in fact, our trial, I think we pride ourselves on the fact that we had a really good representation of African Americans in the trial. In the trial as a whole, 15%, roughly the same between the two arms were black and it was higher when you just looked at the US population.

When you look at the dialysis type of randomisation, it was close to 90%, specifically 89% were on haemodialysis and 11% on peritoneal dialysis. It's very, very much similar to what you see on patients who are being treated with different dialysis modalities.

When you look at history of cardiovascular disease, about 45% in both arms had a history of cardiovascular disease – very similar. Over 90% had a history of hypertension, and about 40% of patients had a history of diabetes.

Remember that when we take care of patients, about 35 to 40% of patients are diabetic as the cause of the kidney failure, and so I think – and this was again obviously reviewed carefully by the *Journal*, I think the population is very typical of what you see.

I can't speak to the other trial, the vada trial because I wasn't involved in that, but I think very comfortable with the idea that our population are typical of what we see in dialysis patients, that I see when I go around in the dialysis unit in Boston, or whether you go around

in a dialysis unit in London in the UK, and I think that, therefore, these results are generalisable.

With respect to ESA hypo-responders, about 12% of our patients were hypo-responsive to ESA, and that is roughly what you see now in the population on dialysis.

There are many different ways of defining hypo-responsiveness and I won't bore you with all the different definitions, but we used two definitions and we presented data on the ESA Hypo-Responsive List. There are additional papers that will be coming out that go into that in much more detail.

We found that dapro treatment of ESA hypo-responders resulted in a similar haemoglobin response to that of patients who were treated with dapA protein. The only little difference was that there seemed to be less utilisation of iron in the ESA hypo-responders who were randomised to dapro to those who were randomised to DAPI, and I think this data is in the supplementary section. It is discussed in the primary paper, but in the supplementary appendices that are presented with the paper and are published on the Journal's website.

Hal Barron: Thank you, Dr Singh, and just to put a point on that. Pretty clearly in these trials, the patients on dapro performed as well as the general population, even if they were hypo-responders, which we think is an important point.

Ajay Singh: Yes.

Hal Barron: Luke, do you want to comment on the clinical structure?

Luke Miels: Yes, I will just do that quickly. As I said earlier, Laura, and thank you for the question, we see two-thirds of the revenue at peak being non-dialysis, so clearly that's a very important component for the product.

In terms of the LDOs in the US, obviously subject to approval, we have already initiated discussions and they are going quite well. I think you should assume they are in the bundle. I think we get a lot of questions around key TDAPA timeframes and ATPCS timeframes, so I think if you just, as a rule of thumb, assume around nine months or three calendar quarters after the FDA approval.

Hal Barron: Thanks, Luke. I know it is the top of the hour, but let's see if we can get a few more questions in. Just because we are running a little late we have six more queued, so operator, can we have the next question?

Emmanuel Papadakis (Deutsche Bank): Thanks very much, and I will try to keep it short. Dr Singh, thank you for the presentation. Perhaps a quick one for you, based on the totality of evidence to what extent do you believe the safety profile of daprodustat is definitively differentiated to roxadustat and vadadustat? We have seen a lot of data for all three of those molecules now.

What do you think the probability of an Advisory Committee is recommending this non-dialysis approval, and assuming it does, perhaps you could just give us what in terms of your practice or you think representatively in the US you think the likely percent of utilisation in that population would be if it had a black box? Thank you.

Hal Barron: Why don't we just go right to Dr Singh on the totality of data relative to what's out there?

I should say just before we start, given that's it a first-in-class potential approval, we are expecting that there be an Advisory Committee, so we are preparing for that, but, Dr Singh, I don't know if you have any comments on how this data does or does not compare with the prior trials and prior agents in a similar class? Then, you can follow-up on how you see this, if approved, impacting your practice.

Ajay Singh: I am not going to try to make comparisons because I think that these are different molecules and the trials were designed differently, and there isn't enough time for me to go through every single decision on these, but I think we are very comfortable with our data suggesting that our goal was to demonstrate non-inferiority to comparator ESA, and I think we did that and I am very proud of it. I think I am proud of the fact that we did really well-conducted trials where we essentially nailed down virtually every patient, so we didn't really have unknown information sitting out there, so we didn't know what happened to patients, etc., that were randomised on the trial. All of that, to me, suggests that we have a very robust programme, and we have presented, I think, very detailed information, both in the papers, but also in the supplementary appendices.

If I had a crystal ball and said what, as a nephrologist, would I think would be the place of these agents? I think it is very important to know that we are really under-treating our non-dialysis population. It is very difficult, and I am saying this now putting a clinical hat on, and you asked me what we do in Boston. Patients have a hard time to get physicians to provide anaemia treatment, that's a fact, and this is particularly so in the population that seems to be most impacted – African Americans, people who are of low socioeconomic class, etc. - and so I think there's an opportunity, at least in the US, I can't speak for everyone around the world, but at least in the US for us to be able to now start treating these patients who should be treated for their anaemia. That's important.

It's also important to note that when these patients' anaemia is not treated they have quality-of-life issues, and if you can get their haemoglobins up patients are going to feel better and they are going to function more like their normal selves, so I think there is an opportunity there, just speaking as a nephrologist with regards to what I see.

The second is I do think that there is an opportunity potentially to have an agent that might have a potential, or might potentially influence iron parameters. We did see that. It is out there. Their hepcidin levels go down by about 30% very soon after those patients are randomised to dapro, and TIBC levels go up.

We didn't see difference with regards to iron utilisation. I think iron utilisation is very complex, I will be straightforward with you. There was an iron protocol that was applied, and most of these patients are now treated with oral iron, which is where you would see an effect, an hepcidin-induced effect on iron absorption, so I think that more studies need to be done there.

Thirdly, and I am aware of running out of time, but certainly the experiment where you are able to normalise haemoglobin by stimulating natural production of erythropoietin has not been done. That is the next step, and so post-marketing studies, other studies will need to be done to say is it really appropriate to under-treat dialysis and non-dialysis patients' subnormal haemoglobins? Are we going to accept that, or we will ever accept under-treating or inappropriately treating diabetics to a higher blood sugar than what normal people have? I don't think that's acceptable, and I think in the long-term, with my crystal ball, and forgive me for saying it, with a crystal-ball type of metaphor, I think that you are going to want to see whether we can normalise the haemoglobin, and I think the best way to normalise haemoglobin is to use an agent that might naturally stimulate erythropoietin production.

Now, remember, I was the PI and first author of the CHOIR study that resulted in the black-box warning that the FDA put into the label. I am convinced that these patients who had been treated had those side effects not because their haemoglobin rose too high, although that's certainly one of the hypotheses, but because they were exposed to large doses of exogenous erythropoietin, and so I think that that experiment has to be done where we try to normalise with an agent that doesn't result in very high levels of erythropoietin.

I apologise for speaking longer than I should, but I needed to get that out there.

Emmanuel Papadakis: Thank you.

Hal Barron: Thanks, Dr Singh. Emmanuel, let me just add one other comment about the research focus that we had over the years that John Lepore, Head of Research, has really focused on.

There are actually three different forms of the HIF prolyl hydroxylase PHD1, 2, and 3, and each regulates different sets of genes and different tissues. Remember, this is transfixated and transcription factor modulating agent, which is quite unique, and the main isoform that regulates EPO production in the kidney is PHD2, I think. The very small molecules developed that are HIF PH1 modifiers, inhibitors have different specificity against each of the PHD isoforms, and dapro has a very high selectivity for PHD2, so, in addition, we are very careful to ensure that dapro was selected for the HIF-PH as they are involved in erythropoiesis, not if they are not HIF-regulated prolyl hydroxylase, such as collagen prolyl hydroxylase, etc., and that might be in addition to the very, very robust development programme that we have put forward – the things that will differentiate our safety profile from other agents, but both a very robust development plan and the unique aspects of the molecule probably have had an impact on our ability to see so clearly the effect of this impressive agent.

Simon Baker (Redburn): Thank you for taking my questions. Two if I may please. Firstly to Dr Singh, I just wondered if you could give us a little bit more colour on the manifestation and severity of the oesophageal and gastric erosion that was observed. Then secondly, the editorial talked about the regional variations on the safety endpoint with vadadustat, I wonder if you could discuss the regional variations that you saw in these studies – it looks like in ASCEND-D the MACE performance in Western Europe was particularly good, and for ASCEND-ND the US upper confidence interval looked like it was about 1.54. I just wonder if you could discuss the implications of that. Thanks very much.

Ajay Singh: I think there are two points. One is that – and again, I'm not going to dwell on other people's data, but just very briefly with respect to design – we used the same haemoglobin targets across the whole world, whereas in the vada programme they used different haemoglobin targets in different parts of the world, so that was an important geographic difference.

We did look at geography, we did stratify for geography, and there wasn't really anything that I think, when you look at US versus ex-US, there wasn't any difference. Everything else pretty much didn't reach statistical significance, so I'm not convinced that there is any geographical difference.

Just within the nephrologists, I'm not sure I can explain why you made that interpretation. Similarly I think if you use the same haemoglobin target, I think as we did, I'm not surprised at all with that data that shows no difference between US and ex-US, or outside US.

With respect to your other question, with regards to oesophageal and gastric erosions, I think it's important to note that these were relatively mild, what happened in these patients, these erosions were mild, and they were self-limited, and when I looked at the data, looking at what are the sorts of things that happen in these patients, across the map there were lots of little, little things – some patients had upper GI-type dyspepsia, the other patients noticed that there was some GI bleeding – there wasn't any pattern to it.

I do think that people need additional investigation here because the numbers of patients were relatively small, and I think that we pointed that out, and it was disparate between the two trials, between the D trial and the ND trial. I think it was seen, I think it was important to state what we saw, and I think it's important to also say that we need additional studies to investigate that further.

Hal Barron: Thank you very much, Dr Singh, and I'd just like to point out that with the gastric erosions too, small numbers and disparate data in each of the trials within the dialysis, there was a trend towards it being less, actually, with ... so it's small numbers, but something to look into.

Kerry Holford (Berenberg): Thank you. On commercial infrastructure, Luke, you mentioned you would leverage your *Benlysta* position - should we expect any significant incremental spend required to launch dapro, assuming it's approved? Can I ask you for clarification on the number of reps you mentioned, I think it was 900 – are those already on board promoting *Benlysta*, or is that the total you would need to increase to?

My second question is on the rate of increase in haemoglobin: you reference what I saw in the paper a faster increase in haemoglobin noted in the dialysis trial versus ESA during the first four weeks of therapy, is that an important differentiating point in the clinic, do you expect that to work in your favour in discussion with regulators, or are there in fact any potential risks associated with such rapid change in haemoglobin? Thank you.

Hal Barron: Thanks Kerry. Luke, why don't you go ahead with the sales question.

Luke Miels: 900, Kerry, is the total number of speciality-care hires that we've made, so that includes *Benlysta*, the oncology business, expansion to *Nucala*, so essentially

the argument there is we've been able to rapidly increase the number of people who are highly qualified versus a history in selling small molecules in plastic containers to primary care physicians.

In terms of spend, I think in aggregate on the P&L, no, it's not going to be an impact, but clearly we'll reallocate between resources that we have in other products, but I would expect that we would invest heavily behind this product at the time of launch to ensure maximum uptake.

Hal Barron: Thanks Luke, and Dr Singh, could you briefly comment on the importance of the rapid rate of increase in haemoglobin relative to epo in the study?

Ajay Singh: We did not see a rapid rise in haemoglobin in our patients in the D or the ND trial between the two groups. I think in part that likely reflects the fact that we have a protocol that was really effective in controlling haemoglobin in patients who were randomised to either dapro or darbe. Obviously I can't speak to what other trials did.

I will point out that ten years ago I published an editorial in CJASN which in very great detail discussed the haemoglobin rate of rise issue when the FDA commented about this with respect to this with CHOIR data, where I published the CHOIR data, and it was analysed in the briefing document and I got into lots of discussions with the FDA, you can see that in the editorial.

It's important to note that it's not just the rate of rise of haemoglobin, it's haemoglobin flexes and so rate of rise, the FDA invoked that as potentially very important but also rate of fall in haemoglobin could be important. It's complex because these are post-doc analyses, they have not been published generally, and they're open to a lot of confounding, and confounding especially by indication.

I think we will need a lot more studies, and I think clearly, discussion on rate of rise, but it wasn't seen in our study, in the data that we've reviewed so far.

Hal Barron: Thank you, Dr Singh, and thank you, Kerry. Why don't we do one last question, then end.

James Gordon (JPM): Hello, thanks for taking the questions – a couple on pre-dialysis and safety, and then then just one about the pitch and dialysis. In the pre-dialysis, why do you think the dapro does look a little bit worse than the ESA on safety, and then the other way round for dialysis – do you think there is a real difference in terms of how patients are pre-dialysis, or dialysis patients actually respond to the drug, or do you think it's just noise and should be ignored?

Then just any regulatory concerns about the on-treatment analysis, that 1.4 hazard ratio – could that be a concern as well? Those were the questions on safety.

The other question was just, in dialysis, if your patient who's not an ESA hypo-responder and not a home dialysis patient, what is the pitch for using a HIF in that population, please?

Hal Barron: Dr Singh, do you want to take the difference in safety profiles in non-dialysis versus dialysis, and maybe just reiterate some of the comments made earlier on the on-treatment analysis. Then Luke, I don't know if you want to make any final comments on the commercial aspect of the last component, and then we'll wrap up.

Ajay Singh: I never want to say never to anything, you made a very strong statement. I think the most important thing to know is that the trials were designed to show noninferiority in an ITT population, and the intention-to-treat population, which is the way these trials are generally done, and certainly were done with respect to what the regulators wanted and what I think the journals now clearly indicated the way to do these trials that we achieve noninferiority, and I think that's important, and then now to compare what you are seeing in non-dialysis and dialysis, I don't want to say anything isn't on us, I never say that, but it doesn't concern me because I think it met noninferiority, that is why you do these trials.

With respect to the on-treatment, I think we have gone through that in some detail. I think on-treatment is not the same as intention-to-treat. Intention-to-treat is the way you do these trials so that you do a randomisation, you balance the cofounding effects, and then you look at the impact of the intervention when you balance these other confounding factors and covariants, and I think when you do it that way you don't see the results you see with on treatment, and I think that's important to realise.

It wasn't something that the reviewers or the journals were concerned about, and I think that's also important to know, so I am pretty sanguine about the fact that dapro is comparable to ESA in both populations and was tolerated with no additional safety signals. I think that is my take-home message from looking at the data in detail, as someone who has been doing this for many years.

Hal Barron: Thank you, Dr Singh. Luke, do you want to comment on the non-dialysis rationale?

Luke Miels: Sure. I think it was the dialysis if I heard James correctly, but feel free to correct me if I am wrong.

James, it is important to look at the total context here. If you look there's a payment under the bundle it is about \$231, so if you do have one in ten, or 12% of patients who are

using very high volumes there, that is going to have an economic consequence for these LDOs, and, of course, we can contract across all patients, so I think we, as our initial discussion, can construct something quite attractive there in terms of relative to EPO.

I think if you look at it versus vadadustat and roxadustat, I suspect this drug, some of the uptake in Japan you have got the simplicity of switching, but you've also got the DDI. If you look at roxa, and, again, this is not necessarily saying this will happen in the US, but you have got to avoid oral iron and phosphate binders one hour before, with statins as well, two hours with vada between phosphate binders and/or iron, and you need to do liver monitoring with statins, so these are all elements we think that we can assemble arguments for these LDOs to contract and be interested in interacting with us.

Hal Barron: Thank you, Luke. Why don't I just wrap up. Thanks, everyone, for attending, and just to say again, we are very excited about the dapro programme, the dapro molecule. It is a very unique molecule, as I highlighted, a very robust development programme, quite compelling data, and most importantly, I think, as you have heard repeatedly, the unmet need is quite significant both in dialysis, and particularly in non-dialysis for those patients with chronic kidney disease and anaemia who actually get nothing and have significant fatigue.

I want to end by thanking our own internal team for a terrific job over many years on bringing this to fruition, and I thank Dr Singh for a great job presenting the data and for helping us with the design and implementation of what will likely be a very transformational medicine, so a great job to everybody.

Thank you very much for taking the time and we will end on this note.

[Ends]