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18th February 2014

Dear Jeremy,

Many thanks for agreeing to consult further on the enzalutamide Final Appraisal Determination (FAD) as a second Appraisal Committee Document (ACD). Astellas appreciates the opportunity to provide our considered response below, comprising an executive summary, a clarification request, our response to the three ACD consultation questions, and a conclusion.

Executive Summary

- Consistent with the declared favourable benefit/risk assessment by the European Medicines Agency and the approved Summary of Product Characteristics, Astellas is of the view that enzalutamide should be recommended by NICE for all adult men with metastatic castrate-resistant prostate cancer (mCRPC) whose disease has progressed on or after docetaxel therapy.

- There is no proper basis for NICE to restrict the conditions of use to prior abiraterone recipients for the three reasons given below. Moreover, Astellas is troubled to have received the proposed restriction without proper notice.

    - Firstly, as abiraterone is also licensed for treating patients **before** chemotherapy, we believe that the recommendation is inconsistent with the declared procedure for conducting a Single Technology Appraisal (" STA"), which is designed to appraise a single product, and not to make judgments across multiple indications. Patients receiving abiraterone for **any** indication would be unjustifiably denied access to enzalutamide based on the current wording of the recommendation.

    - Secondly, we believe that the recommendation is not in line with the agreed final scope of this appraisal, which has been the subject of consultation with relevant Stakeholders. In any event, patients treated with abiraterone had not previously been identified by NICE as a relevant subgroup. This subgroup was not defined at the scoping meeting or at either Appraisal Committee ("AC") meeting, despite being proposed as a group who would welcome the opportunity to receive enzalutamide by the patient representative at the first AC meeting and by both patient and physician representatives' written responses to the first Appraisal Consultation Document(" ACD").

    - Thirdly, while we do not agree with the validity of the proposed restriction by NICE, evidence is emerging to describe the positive response rate of prescribing enzalutamide in patients previously treated with abiraterone. Given that some patients within this subgroup have clinically significant responses to enzalutamide treatment, we believe that clinicians and indeed patients should be given the opportunity to access

enzalutamide, given its "step change" mode of action, and administrative benefits in this final stage of the disease. Otherwise, the appraisal could not properly be characterised as evidence-based.

- The current proposal to preclude use of enzalutamide from all patients who have tried abiraterone both pre- and post-chemotherapy has an effect of denying a much larger proportion of eligible patients than the previous ACD had described. This decision does not reflect the available evidence; is inconsistent with the declared NHS Constitution guiding principles and values to deliver healthcare services in the best interests of patients; and is not an appropriate decision for an STA given that it sets a complicated precedent for future appraisal of drugs which may be used sequentially with their comparators.

Clarification

Prior to answering NICE's specific consultation questions we would like to clarify a key concern relating to the justification of the abiraterone restriction detailed in section 4.22 of the second ACD. Specifically, we are seeking disclosure of the scientific evidence underpinning the statement as highlighted below.

> *4.22 On the basis of the considerations in sections 4.19–4.21, the Committee considered that the magnitude of the additional weight that would need to be assigned to the QALY benefits would justify enzalutamide being recommended as a cost-effective use of NHS resources for patients who have received 2 or more chemotherapy regimens. However, the Committee was aware that patients in this subgroup in AFFIRM had not received previous treatment with abiraterone and the Committee had not seen evidence about the sequential use of abiraterone and enzalutamide. Because of this, the Committee agreed that the evidence it had considered for the subgroup could not be generalised to patients who had previously received abiraterone. The Committee concluded that enzalutamide could be recommended as an option for treating hormone-relapsed metastatic prostate cancer in adults whose disease has progressed during or after docetaxel-containing chemotherapy, only if they have not had treatment with abiraterone and the manufacturer provides enzalutamide with the discount agreed in the patient access scheme.*

In Astellas' considered assessment, no patients in AFFIRM (which is the dataset underlying the clinical effectiveness assessment) had previously received abiraterone, as it was not licensed prior to the start of this trial. Therefore, it is not clear to us the evidentiary basis for NICE to first consider this subgroup as falling within the term "two or more chemotherapy".

The wording of the ACD could be interpreted as NICE classifying abiraterone itself as a chemotherapy option. However, this is not the case. Abiraterone is not a cytotoxic agent, but a hormonal one, and as such, should not be included under the term 'chemotherapy'.

When Astellas presented evidence to broaden the initial recommendation for enzalutamide use in patients whose "*disease has progressed during or after 1 docetaxel containing chemotherapy regimen*" we were asking for a recommendation in patients who had received two or more courses

of **cytotoxic** chemotherapy (such as docetaxel). This was the agreed scope of the STA, and there is no proper basis to extrapolate this to include a hormonal therapy.

If NICE has classified abiraterone as a cytotoxic chemotherapy, then Astellas contest that this is not a satisfactory (nor is it scientifically valid) interpretation of the available evidence.

Astellas Response

Having reviewed the second ACD sent on January 21st, Astellas are pleased that NICE has recognised the value of enzalutamide in patients regardless of the number of prior chemotherapy courses which they have been prescribed. However, we have significant concerns regarding an unexpected change to the first ACD recommendation, specifically, the restriction of enzalutamide in patients who have previously had treatment with abiraterone.

Has all of the relevant evidence been taken into account?

1. Astellas believe that all of the evidence relating to the final scope of this appraisal has been taken in to account.

   We maintain that evidence to support sequential use of abiraterone and enzalutamide is outside of that requested in the final scope. In any event, there is no evidence to support this restriction. However, given that this has now been raised by NICE, Astellas would like share the results of several small investigator led studies looking at sequential use of enzalutamide and abiraterone. This data had not previously been shared because we considered it to be outside of the appraisal scope, and because much of the data was not available until February 2014. These studies have very small patient numbers and no control arm and as such do not offer an opportunity for a full analysis. The studies (summarised in Table 1 below) do however demonstrate that a sizable number of patients experience a PSA response when given enzalutamide after abiraterone. Astellas therefore believe that restricting enzalutamide from patients previously treated with abiraterone, denies them the opportunity to benefit from such a response. Given that enzalutamide is a clinically effective treatment option, it is consistent with the NHS Constitution to place patients in the centre of the NHS, and for doctors to prescribe what is clinically appropriate in the interests of patients under their care. Therefore, it is for the treating doctors to make an informed decision on which treatment option should be prescribed, taking account of the individual circumstances of the patients.

2. The results presented in Table 1 also suggest that the differences in MoA of the drugs have not been adequately interpreted by NICE. Enzalutamide and abiraterone have different modes of action, and as such patients have been shown to respond differently to either drug. Section 4.17 describes the Committee's view that enzalutamide has "*a different mechanism of action from other anti-androgens*" and is a "*step change compared with other androgen receptor blockers*".

   As such, it follows that sequential use of enzalutamide following abiraterone may be an effective treatment choice, or alternative, based on the different mode of action or suitability to the individual patient's needs or preferences.

   Again, this argument supports giving clinicians freedom to select a treatment option based on their individual patient's response and preferences, as is the case with every other currently available therapy for the treatment of mCRPC, whether it is managed through baseline prescribing or the Cancer Drugs Fund.

Table 1 - Summary of enzalutamide efficacy in patients previously treated with abiraterone

Author	Title	Citation	Population/ methods	PSA response results	**Conclusions** (directly quoted from the publications)
Schrader AJ, et al.	Enzalutamide in Castration-resistant Prostate Cancer Patients Progressing After Docetaxel and Abiraterone	Eur Assoc Urol 2013. Epub ahead of print. doi: 10.1016/j.eururo.2013.06.042	• Retrospective analysis • 35 total patients all previously treated with abiraterone • The median duration of abiraterone treatment was 9.0 mo (range: 2.0–19.0 mo). • The median duration of subsequent enzalutamide treatment was 4.9 mo (2.4–7.4).	• Of the 35 patients, 16 (45.7%) achieved a >50% decline in PSA, and 14 (40%) had a rising PSA as the best response. • Median time to progression was 4.0 mo (95% CI, 2.0–6.0) for 18 of 35 patients with at least one declining PSA value while taking enzalutamide (51.4%).	Enzalutamide treatment achieved only a modest response rate in patients progressing after abiraterone. Although cross-resistance between abiraterone and enzalutamide was a common phenomenon, it was not inevitable, and a small but significant number of patients showed significant benefit from sequential treatment.
Bournakis E, et al.	Enzalutamide (ENZA) in heavily pretreated patients with bone metastatic castration resistant prostate cancer (mCRPC) resistant to androgen biosynthesis inhibitor (ABI) treatment - the Hellenic experience of the Name Patient Access Program (NPAP)	ECC 2013. Poster presentation P413.	• Retrospective analysis • 25/35 patients treated with enza had received prior ABIs [Abiraterone Acetate 20, Orterenol 7, (Both 2)].	• To date of publication, maximum PSA decline ≥50% is observed in 6/15 (40%) patients	ENZA is well tolerated in a cohort of heavily pretreated far advanced m-CRPC patients and appears in this preliminary report to benefit a subset of pts resistant to prior ABI treatment. Further follow up and a planned molecular characterization of archived bone marrow infiltrating tumors will help guide selection of this population.
Bianchini D, et al.	Antitumour activity of enzalutamide (MDV3100) in patients with metastatic castration-resistant prostate cancer (CRPC) pre-treated with	Eur J Cancer 2013; doi: 10.1016/j.ejca.2013.08.020 [Epub ahead of print].	• Retrospective analysis • 39 patients with metastatic CRPC were identified for this analysis	• Overall 16 patients (41%) had a confirmed PSA decline of at least 30%. • Confirmed PSA declines of P50% and P90% were achieved in 5/39 (12.8%) and 1/39 (2.5%) respectively. • Of the 15 patients who responded to	Our preliminary case series data suggest limited activity of enzalutamide in the post-docetaxel and post-abiraterone patient population.

	docetaxel and abiraterone		(median age 70 years, range: 54–85 years)	abiraterone, two (13.3%) also had a confirmed P50% PSA decline on subsequent enzalutamide. • Among the 22 abiraterone- refractory patients, two (9%) achieved a confirmed P50% PSA decline on enzalutamide.	
Thomson D, et al.	Enzalutamide post docetaxel and abiraterone in metastatic castrate resistant prostate cancer (mCRPC): results from an expanded access programme	BAUS 2013.	• Retrospective analysis • 23 total patients (all previously treated with docetaxel and abiraterone)	• Nine (39%) patients showed sensitivity to enzalutamide, defined as >50% reduction in PSA.	To our knowledge, this is the first UK data to demonstrate enzalutamide shows activity post docetaxel and abiraterone in mCRPC. In this cohort, the effectiveness was more pronounced in those sensitive to abiraterone.

Heather H. Cheng et al	The effect of prior abiraterone (Abi) use on the activity of enzalutamide (Enza) in men with mCRPC.	J Clin Oncol 32, 2014 (suppl 4; abstr 18)	• Retrospective analysis
			• 195 total patients
			• 150 previously treated with abiraterone
				• 42% (76 of 183) of Enza-treated patients achieved a 30% or greater PSA decline
				• 39% (58 of 150) response among prior Abi-treated patients
				• 55% (18 of 33) response in Abi-naïve pts
				• Of 79 patients who lacked significant response to prior Abi:
				  • 30% (25 of 79) achieved a 30% or greater PSA decline
				  • 19% (15 of 79) achieved a 50% or greater PSA decline with subsequent Enza.
					While the activity of Enza appears to be blunted in the post-Abi setting, PSA declines still occur in a meaningful proportion of patients. Notably, 30% of patients without significant response to prior Abi responded to subsequent treatment with Enza, suggesting a subset of men with distinct biological resistance pathways.

Robert Stevenson et al	The sequential use of abiraterone and enzalutamide in metastatic castrate resistant prostate cancer patients: Experience from seven U.K. centers.	J Clin Oncol 32, 2014 (suppl 4; abstr 125)	• Retrospective analysis • 79 total patients • 75 previously treated with abiraterone • 62 of these patients receiving Abi as the last treatment prior to Enz	• At the time of submission 55 patients had stopped Enz due to PSA progression with a mean TTP of 15.87 weeks and 28 patients had died.	The AFFIRM study demonstrated TTP of 36 weeks in patients post-docetaxel. In this audit of patients receiving Enz post-Abi the TTP was only 15.87 weeks, suggesting possible reduced efficacy in patients receiving Enz post-Abi and docetaxel. Trials are underway comparing Abi alone or in combination with Enz which may improve efficacy

Francisco Emilio Vera-Badillo	Clinical activity of enzalutamide against metastatic castration-resistant prostate cancer (mCRPC) in patients who have progressed on abiraterone acetate: The Princess Margaret experience.	J Clin Oncol 32, 2014 (suppl 4; abstr 159)	• Retrospective analysis • 26 patients previously treated with abiraterone • Median duration of previous abiraterone was 8.7 (range 1.4-22.7) months.	• Seven pts (27%) had a PSA response ≥ 50% and an additional 7 patients (27%) had a ≥ 30% PSA response. • Median TTF on enzalutamide was 4.9 (95% CI 3.8-6.2) months.	Treatment of patients with mCRPC with enzalutamide after progression on docetaxel and abiraterone has modest clinical activity.
David Thomson	Enzalutamide after failure of docetaxel and abiraterone in metastatic castrate resistant prostate cancer (mCRPC): Results from an expanded access program.	J Clin Oncol 32, 2014 (suppl 4; abstr 188)	• Retrospective analysis • 23 patients previously treated with abiraterone • (other relevant prior treatments included cabazitaxel (35%), dexamethasone (30%), and stillboestrol (52%))	• Nine (39%) patients showed sensitivity to enzalutamide, defined as a greater than 50% reduction in PSA. • There was a correlation between PSA response to abiraterone and enzalutamide (R=0.45, p=0.03). • In 10 out of 23 and 13 out of 23 patients who were sensitive and insensitive to abiraterone, 60% and 23% had a great than 50% reduction in PSA, respectively.	Enzalutamide has activity following failure of docetaxel and abiraterone in mCRPC. The effectiveness is more pronounced in those who have responded to abiraterone.
M. Andreas Roeder	Biochemical response to enzalutamide therapy in patients with mCRPC following docetaxel and abiraterone treatment.	J Clin Oncol 32, 2014 (suppl 4; abstr 202)	• Retrospective analysis • 24 patients previously treated with abiraterone	• Forty-six percent of patients had a greater than 30% decrease in PSA. • The PSA response to enzalutamide did not correlate to the number of prior cancer treatments (p = 0.57), time from diagnosis to CRPC (p = 0.11), or prior response to docetaxel (p = 0.67). • Eight patients treated with second line cabazitaxel had an inferior PSA response to enzalutamide (p = 0.03), and there was a trend for the PSA response to abiraterone to correlate with the PSA response to the succeeding enzalutamide (B = 0.22, p = 0.05).	Patients with post-chemotherapy, post-abiraterone mCRPC treated with enzalutamide showed less marked biochemical response to therapy compared to the results from the AFFIRM study where post-chemo abiraterone was not used. Whether this is an effect of cross-resistance or a result of the natural history of the disease needs further elaboration.

Gurprataap Singh Sandhu	Enzalutamide after abiraterone in patients with metastatic castrate-resistant prostate cancer (mCRPC).	J Clin Oncol 32, 2014 (suppl 4; abstr 240)	• Retrospective analysis • 23 patients previously treated with abiraterone 15 patients had received prior docetaxel chemotherapy	• Median duration of abiraterone and enzalutamide treatment was 7 and 4.5 months respectively. • 12 patients had at least one declining PSA value post enzalutamide treatment, with 5 patients showing >25% decline in PSA and 4 patients > 50%. • Median time to PSA progression in patients receiving enzalutamide following abiraterone was 2.3 months.	Sequential enzalutamide in patients with CRPC post-abiraterone showed only modest activity, indicating that the clinical benefit of sequential use of highly potent androgen pathway inhibitors cannot be assumed, and should be measured in prospective studies.

Mark Creamer Scholz	Enzalutamide in men with prostate cancer resistant to docetaxel and abiraterone.	J Clin Oncol 32, 2014 (suppl 4; abstr 247)	• Retrospective analysis
			• 66 total patients (all previously treated with abiraterone)
			• 63 evaluable for PSA response
			  • 55 men received previous docetaxel
			  • 38 had received previous Provenge
				• After a median follow up of 12.5 weeks, 18(29%) men met criteria for (30%) PSA response. 13 (21%) men had stable disease and 32 (51%) men had PSA progression.	Enzalutamide has activity in a heavily pre-treated population of men resistant to abiraterone and docetaxel.

Sushil Badrising	Clinical Activity and Tolerability of Enzalutamide (MDV3100) in Patients With Metastatic, Castration-Resistant Prostate Cancer Who Progress After Docetaxel and Abiraterone Treatment	Cancer Month 00, 2013	• Retrospective analysis • 61 total patients (all previously treated with abiraterone) • The median duration of Enz treatment was 14.9 weeks (IQR, 11.1-20.0 weeks)	• 13 patients (21%) had a maximum PSA decline ≥50%. • The PSA response to Doc and AA did not predict the PSA response to Enz.	Enz has modest clinical activity in patients with metastatic, castrate-resistant prostate cancer who previously received Doc and AA. PSA response to Doc and AA does not predict for PSA response to Enz.

Sebastian Christoph Schmid	Enzalutamide After Docetaxel and Abiraterone Therapy in Metastatic Castration-Resistant Prostate Cancer	Adv Ther DOI 10.1007/s12325-014-0092-1	• Retrospective analysis • 35 total patients (all previously treated with abiraterone) • The median treatment duration on enzalutamide was 2.8 months.	• The median overall survival was 7.5 months [95% confidence interval (CI) 4.7–10.3] • Median progression-free survival assessed by imaging was 3.1 months (95% CI 1.4–4.8).	Although the results are limited by a small patient number, the consecutive use of enzalutamide and abiraterone after taxane-based chemotherapy shows a modest clinical activity. Thus, sequence therapy alternating between chemotherapy and antihormonal drugs might be a more promising approach in mCRPC treatment

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

3. For the reasons given above, we do not agree with the validity of restricting the clinical use of enzalutamide to patients who have received abiraterone. This restriction does not have a proper pharmacological basis, nor is it evidence based. This consideration may be borne out of NICE's misclassification of abiraterone as a cytotoxic chemotherapeutic agent, unless NICE advise us otherwise. We would also like to further discuss the implications of basing a restriction on the use of abiraterone, which is licensed for two indications. The current wording will restrict access to patients who have used abiraterone in both the pre- and post-chemotherapy settings.

   Moreover, without prejudice to our disagreement with the restricted conditions of use, the proposed recommendation does not provide any clarity to inform the prescribers the clinical circumstances in which enzalutamide can be prescribed. It is not clear what "*had treatment with abiraterone*" means in clinical practice. Patients may have tried abiraterone and discontinued due to tolerability, compliance or efficacy issues. Patients may therefore be denied access to enzalutamide having not had a positive response to abiraterone.

   As discussed before, if the guidance is intended to describe all abiraterone indications, then we are of the view that the guidance is not consistent with the agreed scope of this appraisal which had been the subject of consultation with the relevant Stakeholders, and the declared procedure for an STA.

   According to the published procedural guidance, the remit of an STA is to review a single drug within a single indication[1]. According to NICE's procedure, there is no basis to perform a cost-effectiveness analysis across two indications (pre and post chemotherapy), or an analysis of sequential use in the post-chemotherapy setting where it is not within the agreed scope of the STA. Such an analysis would require the identification of sequential comparators and/or the inclusion of patients from earlier in the treatment pathway Indeed, it is procedurally unfair to do so without proper consultation and notice to Astellas.

   The scope of this appraisal was to review post-chemotherapy use of enzalutamide, in line with the approved therapeutic indication set out in the Summary of Product Characteristics as it underpins Astellas' legal right to market the product. The appraisal should be based upon the evidence derived from the AFFIRM trial. Therefore, provided that the patient has received docetaxel treatment prior to enzalutamide, it is beyond the remit of an STA to seek evidence on the sequential effect of enzalutamide with *any* drug used in an earlier indication as this will fall outside of the approved therapeutic indication and the evidence underlying the centralised approval.

   As already explained, it is critical to understand that this restriction unjustifiably denies access to enzalutamide for a larger number of patients than were initially deemed eligible in the first ACD. In a recent press release[2], NICE offered a clarification that "*The second Appraisal Consultation Document (ACD) published last week has actually widened the population for which enzalutamide has been recommended*." This statement appears to reinforce our assertion that

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[1] http://www.nice.org.uk/aboutnice/howwework/devnicetech/developing_nice_technology_appraisals.jsp

[2] http://www.nice.org.uk/newsroom/features/BehindTheHeadlinesProstateCancerDrugDecisionACruelTwist.jsp

NICE have not considered patients treated with abiraterone prior to chemotherapy. The outcome of the appraisal could not, in our respectful view, be considered as fair and objective.

4. Astellas would like to understand why patients previously treated with abiraterone have drawn more attention than patients treated with other similarly indicated drugs, or other subgroups excluded from the trial design.

   Evidence from AFFIRM cannot inform an evaluation of efficacy of enzalutamide if used sequentially with treatment alternatives because the trial was not designed to generate this kind of data. As with a majority of clinical trials, the exclusion criteria for AFFIRM required that patients should not have had prior treatment with drugs which may confound the true safety and efficacy of enzalutamide. Patients were excluded if they received prior ketoconazole, sipuleucel-T, concurrent anti-androgen therapy, or herbal products known to affect PSA levels, and would not have received either abiraterone or cabazitaxel as neither was licensed prior to the start of AFFIRM. As such we do not understand why abiraterone has been specifically restricted in this way. We are of the opinion that this ad hoc approach to restricting the therapeutic use of an effective treatment sits uncomfortably with the European regulatory framework and the NICE health technology appraisal procedure where the decision-making should be evidence-based taking account of the clinical relevance and the external validity of the submitted study data, where the study population should be suitable for extrapolation to the population to be treated. .

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

5. It appears that NICE's last minute decision (without proper notice or proper consultation) to focus on the abiraterone subgroup was taken due to cost-containment considerations if both abiraterone and enzalutamide are allowed to be used in the NHS. As sequential use was not specified in the final scope, a cost-effectiveness analysis of this scenario has not been presented, and due to the nature of data in this field, it would not have been possible to conduct such an analysis to NICE standards. The adopted approach is procedurally unfair to Astellas.

   This subgroup was not defined at the scoping meeting or at either Appraisal Committee meeting, despite being proposed as a group who would welcome the opportunity to receive enzalutamide by the patient representative at the first AC meeting and by both patient and physician representatives' written responses to the first ACD. Further, the committee were openly asked of any relevant subgroups of interest, with none being identified, and positive comments were made by Stakeholders regarding the omission of any restriction relating to abiraterone.

6. We strongly support providing clinicians a choice of authorised therapeutic alternatives that would be most appropriate for the mCRPC patients under their care, taking account the patient's individual clinical circumstances . The "step change" mode of action and administrative benefits of enzalutamide should be available to all patients regardless of prior treatment, and we believe that clinicians are best placed to make such decisions based on their knowledge of, and relationship with, the individual patient.

   Enforcement of the current recommendation is not compatible with the NHS Constitution which places patients at the heart of the choice of treatment pathways, and prejudices mCRPC patients' rights to effective treatment options, particularly those who have received abiraterone.

The policy if not corrected discriminates against mCRPC men and is incompatible with the equal treatment principle because in relation to women, clinicians have been given more clinical freedom to access to licensed cancer treatments without such "sequential restrictions", allowing them to make more appropriate choices for their patient.

Conclusion

In conclusion, we submit:

1. We are troubled by the late decision to restrict the use of enzalutamide to patients who have previously been treated with abiraterone without proper notice, and believe that both the remit and the scope of this STA has been exceeded.

2. The proposed restriction is much broader than the restriction proposed in the first ACD, and will deny access to enzalutamide in many more men, including those who have accessed abiraterone via the Cancer Drugs Fund.

3. The decision does not reflect the available data and hence is not evidence-based.

4. The proposed guidance is incompatible with the equal treatment principle in that prostate cancer patients do not have the same right as female cancer patients.

We are aware that the introduction of this restriction has led to considerable discontent amongst Stakeholders, in part because it is not clear how this restriction is related to the evidence presented following the first ACD, in part, because Stakeholders had not previously had a chance to debate this restriction, and in part, because abiraterone is also licensed for use in patients prior to treatment with docetaxel.

Astellas are committed to continuing an open and transparent dialogue with NICE to address these issues to permit timely and equal patient access to this effective treatment option with enzalutamide , and hope that the clarifications and evidence submitted above will allow us to work together and ensure that suitable guidance is given to patients and clinicians as soon as possible.

With kind regards

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