Information Processing Unit
Area 6
Medicines & Healthcare products Regulatory Agency
151 Buckingham Palace Road
Victoria
SW1W 9SZ

22-Nov-2017

EudraCT number: 2017-002329-39
Sponsor reference number: MRC RE06

Dear Colleague,

RE: Renal Adjuvant MultiPle Arm Randomised Trial (RAMPART): An international investigator-led phase III Multi-Arm, Multi-Stage (MAMS), multi-centre, randomised controlled platform trial of adjuvant therapy in patients with resected primary renal cell carcinoma (RCC) at high or intermediate risk of relapse

I am writing in response to the Notice of Grounds for Non-Acceptance letter, dated 08-Nov-2017. In this letter we address each of the points that have been raised and we describe our proposed protocol amendments for your consideration. Dr Angela Meade has discussed the medical points and proposed responses with Dr Maria Beatrice Panico whilst Dr Francesca Schiavone has discussed the pharmaceutical points with Dr Graham McNaughton.

Both 'tracked-changed' and 'clean' versions of the updated protocol are enclosed with this re-submission and a list of additional supporting documentation is presented at the end of this cover letter.

Medical points

1) The Sponsor is required to amend the exclusion criteria for QT interval and exclude patients whose QT interval corrected using Frederica's formula (QTcF) > 450 ms or a rationale must be provided why a QT interval of 470 ms should be considered acceptable in both male and female patients.

The QT interval has been amended to be <450ms for Inclusion Criteria 8 (Section 3.3.1), Table 2 (Screening Procedures) and Section 6.3.2 (Electrocardiogram).

2) The Sponsor is required to amend the protocol and clarify that a serum pregnancy test will be performed to exclude pregnancy at screening. Urine pregnancy test is acceptable after contraception has been established. In case of doubt a urine pregnancy test must always be followed by a serum pregnancy test.

Inclusion criterion 12 (Section 3.3.1) and Table 2 have been amended to only include a negative serum HCG test to confirm patient's eligibility. During the treatment phase and after contraception has been established, a choice of urine or serum HCG testing is included (see Table 14) with a clarification stating that a serum HCG test should be carried out if there is any doubt over the results from a urine pregnancy test. Table 12 has also been updated to reflect the requirement for a urine or serum HCG test throughout the treatment phase.

Each treatment section (Section 5.3.2 and 5.4.2) has been amended to include a reminder on HCG testing prior to treatment administration (new sentence '*Pre-menopausal patients are required to have a negative urine HCG pregnancy test prior to the administration of the trial treatment. A serum HCG pregnancy test should be performed if there is any doubt over the results of the urine test')*.

3) The following statement cannot be considered acceptable: "Not engaging in sexual activity for the total duration of the trial and the drug washout period is an acceptable practice". As stated in the CTFG guidance about contraception "the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject". Considering the long duration of the treatment and washout phases, abstinence for the duration of the trial and the drug washout period is not deemed acceptable. The Sponsor is required to amend the protocol and state that contraceptive measures will apply to all male participants and to women of childbearing potential. The protocol must state that abstinence is acceptable only if it is the preferred and usual lifestyle of the subject.

Section 5.8.4 of the study protocol has been amended to replace the previous statement with the following sentence "*Abstinence is acceptable only if it is the preferred and usual lifestyle of the subject. Occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception*."

4) The Sponsor is required to provide a strong rationale to support inclusion of adult patients whose body weight is 30kg or the body weight inclusion criterion must be amended as appropriate.

The inclusion criterion stating a body weight greater of equal to 30kg has been removed. Exclusion criterion 18 allows clinicians to make a decision to exclude patients for a broad range of reasons, and would include the exclusion of underweight patients: '*Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results*'.

5) It is not expected that the trial toxicity management guidelines are not included in the protocol, but provided separately. The sponsor is required to amend the protocol and include in the protocol the toxicity management guidelines for all treatment arms.

A comparative table of expected side effects for each Investigational Medicinal Product and toxicity management guidelines have now been included in the protocol (Appendix A and B). The toxicity management guidelines contain information which is standard across all AZ protocols investigating durvalumab and tremelimumab.

6) The Sponsor is required to extend the AEs/SAEs collected to at least 105 days after the last study drug administration or a rationale must be provided to support a 90-day duration of safety follow-up.

All participating sites will be required to report adverse events up to Month 15 (approx. 120 days after last protocol treatment for Arm B and C patients); guidance has been updated in Section 7.1 of the protocol to reflect the timelines for AE reporting. AE reporting for patients terminating protocol treatment early will also continue up to 120 days after last protocol treatment.

Remark concerning the durvalumab IB: the Sponsor is reminded that a SAR which occurred once cannot usually be considered expected, unless there is a very strong plausibility of a causal relationship with the IMP and a robust justification based on medical judgement is provided. In the case of this IB single occurrences have to be considered unexpected due to the absence of a strong justification to support their expectedness. The Sponsor is required to acknowledge this remark and

commit reporting single occurrences as SUSARS. The Sponsor is also reminded that in future medical concepts will not be allowed.
Remark concerning the tremelimumab IB: In non-serious adverse reactions are included in the Reference Safety Information (RSI) table the sponsor is reminded that should a serious event occur for any term which has only previously been seen as non-serious this should be considered unexpected and therefore reported as a SUSAR. Single occurrences are unexpected

We acknowledge these points. All participating centres will receive detailed training on safety reporting at site initiation and throughout the course of the trial; both remarks outlined above will be highlighted to participating sites and information will be incorporated in relevant site manual/guidelines.
The trial physician will review all serious adverse events reports received and advise where events should be considered unexpected and report to the MHRA within the required timelines (7 or 14 days).

Remark concerning addition of future arms: the Sponsor is advised to contact the MHRA before submitting an amendment adding additional arms.

We acknowledge this point and will contact the MHRA before submitting an amendment for the inclusion of additional research arms. As outlined in our initial application, the addition of new arms will also be discussed with EMA and FDA prior to implementation.

Pharmaceutical points

1) The QP declaration provided does not refer to the proposed trial. An updated declaration should be provided.

2) The full supply chain to be used in this trial for both IMPs should be confirmed (and all necessary supporting document for these sites submitted MIA (IMP) or QP declaration).

A flow diagram summarising the supply chain for both IMPs is presented in Appendix I of this cover letter; the relevant QP declarations/MIA are also enclosed with this re-submission and summarised in Table 1 of this letter.

I would like to thank you for considering amendments described above. We welcome the opportunity to respond to any further clarification or questions you may have.

Kind regards

Dr Angela Meade

On behalf of the RAMPART Trial Development Group

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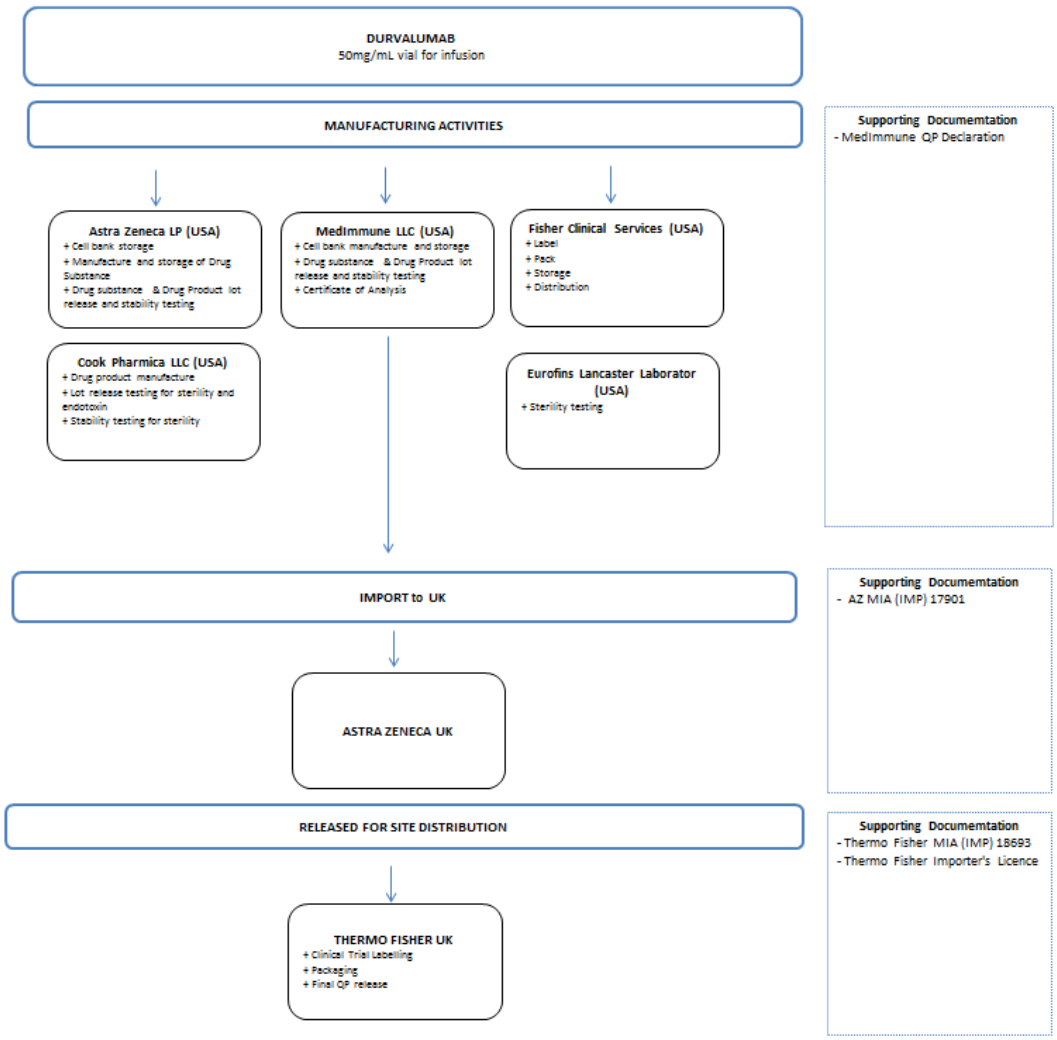
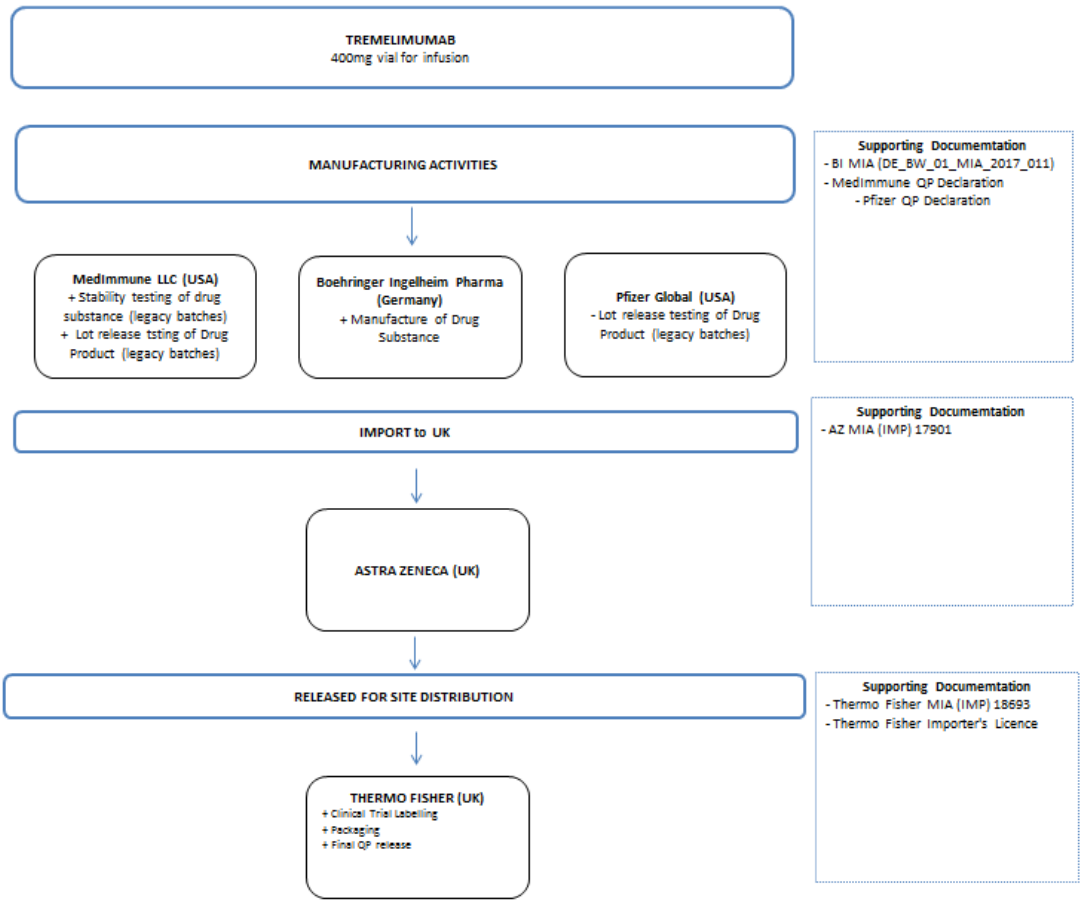
Table 1. Enclosed documentation

Document	Version	Date
Protocol (clean and tracked changes)	1.0	22-Nov-2017
Manufacturer's authorisation (Boehringer Ingelheim Pharma) (tremelimumab)		06-02-2017
Pfizer QP Declaration (legacy batches; tremelimumab)		
MedImmune QP Declaration (tremelimumab)		16-Nov-2017
MedImmune QP Declaration (durvalumab)		16-Nov-2017
Manufacturer's authorisation (AstraZeneca UK)		27-Jul-2017
Manufacturer's authorisation (Thermo Fisher)		13-Apr-2017
Importer's Licence (Thermo Fisher)		15-Feb-2017

APPENDIX I: Supply chain for RAMPART Investigational Medicinal Products (Durvalumab and Tremelimumab)




TREMELIMUMAB
400mg vial for infusion
MANUFACTURING ACTIVITIES
Supporting Documemtation
- BI MIA (DE_BW_01_MIA_2017_011)
- MedImmune QP Declaration
- Pfizer QP Declaration
MedImmune LLC (USA)
+ Stability testing of drug substance (legacy batches)
+ Lot release tsting of Drug Product (legacy batches)
Boehringer Ingelheim Pharma (Germany)
+ Manufacture of Drug Substance
Pfizer Global (USA)
- Lot release testing of Drug Product (legacy batches)
IMPORT to UK
Supporting Documemtation
- AZ MIA (IMP) 17901
ASTRA ZENECA (UK)
RELEASED FOR SITE DISTRIBUTION
Supporting Documemtation
- Thermo Fisher MIA (IMP) 18693
- Thermo Fisher Importer's Licence
THERMO FISHER (UK)
+ Clinical Trial Labelling
+ Packaging
+ Final QP release