Abstract of COGEM advisory reports on the application for a clinical trial testing recombinant *Vaccinia virus*- en *Fowlpox virus*-vaccine in patients with prostate cancer

COGEM advisory report CGM/130617-01 & CGM/130926-01

Summary

Recently, COGEM was asked to advise on an application concerning a clinical trial with the recombinant virus vaccines PROSTVAC-V and PROSTVAC-F. In this trial the applicant aims to evaluate whether the use of these vaccines will improve the live-expectancy of patients with prostate cancer.

In her first advisory report on this application COGEM stated that data were missing, especially those concerning the molecular characterization of the viruses. In order to reduce the risks caused by contact transmission of PROSTVAC-V COGEM considered it essential to put in place additional management measures.

Based on the initial COGEM advisory report the applicant included extra management measures in the Study Subject and Study Staff Instruction Documents. Additional information concerning the molecular characterization of the GMO's was provided.

Upon evaluation of the newly provided information COGEM concluded that the molecular characterization of both recombinant vaccines is still inadequate. The origin of the parental virus TBC-Wy is not unambiguously determined. In order to assess the risks for humans and the environment, a proper molecular characterization of the recombinant vaccine is a prerequisite.

In conclusion, COGEM is of the opinion that these issues need to be addressed before the environmental risk assessment can be completed.

Introduction

COGEM was asked to advise on the application for a clinical trial entitled "A randomized double-blind, phase 3 efficacy trial of PROSTVAC GM-CSF in men with asymptomatic or minimally metastatic, castrate-resistant prostate cancer'. In this trial the applicant aims to evaluate whether the use of the recombinant vaccine PROSTVAC-V/F (± GM-CSF) will improve the live-expectancy of patients with prostate cancer.

Aspects of the recombinant-vaccine

During the clinical trial, two live recombinant poxvirus strains, PROSTVAC-V and PROSTVAC-F will be administered. This may be combined with the adjuvant 'Granulocyte macrophage colony stimulating factor (GM-CSF)'. The applicant claims that the recombinant virus strain PROSTVAC-V is based upon the vaccine strain TBC-Wy of *Vaccinia virus*, and that PROSTVAC-F is based upon the vaccine strain TBC-FPV of *Fowlpox virus*. Both recombinant vaccine strains encode the same four human proteins. The first protein is the Prostate Specific Antigen (PSA), which is specifically expressed in prostate cells. The remaining three proteins are involved in the activation of a T-cell based immune response in humans. These proteins are also known as TRICOM. As a result of the vaccination with PROSTVAC-V/F the applicant aims to break through the tolerance for PSA expressing cells and to initiate an immune response against prostate cancer.

Molecular characterization

The applicant molecularly characterized PROSTVAC-V and PROSTAC-F by means of Southern blot, PCR and sequence analyses. However, the data of the Southern blot and PCR analyses were not provided in the initial application. Therefore, the applicant's conclusions based on these data could not be evaluated by COGEM. The applicant did provide the full genome sequence of both vaccine strains, and compared these with the sequences of *in silico* generated versions of both GMO's. The comparison demonstrated several aberrations between the analysed and *in silico* generated GMO. In addition, COGEM noted that the inserted expression cassette in PROSTVAC-V differed at several points from the one inserted in PROSTVAC-F.

The observed differences and the possible impact of these differences on the characteristics of the GMO's were not explained by the applicant. Based on the provided information COGEM was in her first advisory report of the opinion that the molecular characterization of PROSTVAC-V/F was inadequate and did not meet the criteria laid down by COGEM earlier this year.[1] COGEM considered additional information on the molecular characterization necessary before a final conclusion could be made.

In response to the abovementioned comments, the applicant sent additional information, regarding the molecular characterization of PROSTVAC-V and PROSTVAC-F, including Southern blot and PCR data. Unfortunately, upon evaluation, this information did insufficiently address the previously mentioned concerns. The molecular characterization of the intended modification in PROSTVAC-V and PROSTVAC-F was still inadequate. The impact of the observed differences between: a. the GMO and the *in silico* designed version, and b. the GMO and the parental virus strain were not described.

On top of that, the origin of the parental virus strain (TBC-Wy) of PROSTVAC-V is doubtful. Based on the provided information COGEM could not conclude whether or not TBC-Wy is actually a derivative of Dryvax. Since the environmental risk assessment of the applicant is primarily based on the proven safety of Dryvax, the ancestry of TBC-Wy from Dryvax should unequivocally be demonstrated.

In view of the above, COGEM is of the opinion that, despite the provided additional information, the molecular characterization of PROSTVAC-V/F is insufficient.

Environmental risk assessment

Generally, contact with *Vaccinia virus* causes mild symptoms in humans. However, the virus can also lead to severe, live-threatening illness. In the latter, shedding of the virus may increase which enlarges the chance of contact transmission. In the intended clinical trial measures are taken to limit the contact of the study subject with individuals, who belong to risk groups. Due to these measures, the chance that an adverse effect will occur and the severity of this effect is limited. COGEM notes that the study subjects have been vaccinated against the poxvirus previously. This will reduce replication of PROSTVAC-V and the chance of subsequent shedding of PROSTVAC-V. In addition, the injection-site will be covered with a water-resistant and not-adhesive bandage. Under these conditions COGEM considers it unlikely that contact transmission will occur and result in a severe effect. However, this cannot be excluded completely.

In order to reduce the risks related to contact transmission with PROSTVAC-V COGEM advised in her first advisory report to apply additional management measures. These measures are:

- (Hospital) staff assigned to this trial, should not be part of the risk group of people with an increased chance of contact transmission and/or an increased chance of a serious adverse effect as consequence of contact transmission;
- To prevent eye infections, all individuals who are present in the treatment room should wear safety goggles. COGEM emphasizes the importance that physicians and nursing staff disinfect their hands immediately after administration of PROSTVAC-V;
- The administration should take place in a single patient room according to the guidelines from the "Infection Prevention Working Party" (WIP)[2];
- The study subject and the people in direct contact (including the general practitioner) should be instructed extensively about the procedure to replace and dispose contaminated bandages.

In response to COGEM comments, the applicant included the suggested measures in the Study Staff Instructions and in the Study Subject Instructions documents. COGEM acknowledges in her second advice that the proposed measures were largely included in the renewed instruction documents. However she noted one omission. Apart from the hospital staff, also the study subject should wear safety goggles. This measure was not added to the Study Subject Instructions document. COGEM requested the applicant to adapt the document on this point.

Conclusion

If the applicant complies with the abovementioned management measures, COGEM is of the opinion that the intended clinical trial most likely poses a negligible risk to human health and the environment. Due to the limited molecular characterization of PROSTVAC-V and PROSTVAC-F and due to the lack of clarity about the ancestry of TBC-Wy, COGEM is of the opinion that the application is still incomplete. Until these issues are addressed, COGEM is unable to complete the environmental risk assessment.

Of note, the application filed in the Netherlands contained a surplus of less relevant information, which is jeopardizing its clarity and transparency.

References

1. COGEM (2013). Criteria voor moleculaire karakterisering van ggo's voor medische en veterinaire toepassing. COGEM advies CGM/130227-05
2. Infection Prevention Working Party. http://www.wip.nl/UK/document.htm (04/10/2013)