Biosafety Advisory Council

Secretariat

5 July 2004

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Title: Advice of the Belgian Biosafety Council in response to the letter of 4 June 2004 of the notifier following the authorisation delivered for notification B/BE/03/B3 of the company Transgene for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

Context

The notification B/BE/03/B3 was submitted by Transgene to the Belgian Competent Authority in January 2004 for a request of deliberate release in the environment of genetically modified organisms other than higher plants for research and development according to Part B of Directive 2001/18/EC and the Royal Decision of 18 December 1998.

The dossier has been officially acknowledged on 2 February, 2004.

The planned activity is a clinical trial on cancer patients with a genetically modified adenovirus designed to treat cancer patients. The title of the study is: **"Phase I/II multicentre study of TG1024 (Adenovirus Interleukin 2) in patients with metastatic melanoma or other advanced solid tumor cancers."**. The Belgian patients will be treated at the 'CUB Hôpital Erasme' in Brussels, where Prof. Thierry Velu, Department of Medical Oncology, will be the principal investigator. The study is already running in Switzerland. No other European country is involved in this trial.

The Belgian Biosafety Council has sent its advice (advice of 26 March 2004 with reference BAC_2004_SC_112) on 2 April 2004 to the Competent authority and on 29 April 2004 the authorisation was delivered to the notifier on the conditions proposed by the Biosafety Council in its advice.

On June 4th 2004 the notifier has sent comments to the Competent authority about the conditions of the authorisation and asks to the Council and its experts to alleviate condition 2

[1] revised version of document BAC_2004_SC_145 as approved on 5 July 2004

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where it is required that *'after each injection, the patients stays at least 24 hours in an individual room at the hospital until the level of viral vector in his body fluids has begun to decrease'*. The notifier accompanies his request with data about 'Viral Dissemination in Blood in Patients receiving Repeated Injections of Ad-IL2 (Clinical Study Referred TG1042.01)' and 'Adenoviral Detection in Biological Fluids of Patients Treated with Ad-IFNγ in the Phase I Clinical Study Referred TG1042.01'. These data were already present in the original dossier acknowledged on 2 February 2004.

In a letter dated of 10 June 2004 the competent authority asks the advice of the Council on the above question of the notifier and on the biosafety implications of the new protocol amendment (amendment nr. 5) that was also notified on June 4th, 2004.

Scientific evaluation

The previous scientific evaluation (see expertise report accompanying the advice of 26 March 2004 - ref: BAC_2004_GT_111) concluded that:
- If present, the low number of virus particles that become excreted may infect a few cells of the persons that are in contact, and that this will cause no problem. No new virus will be produced and the low doses of IL2 that could be produced will cause no harm.
- However, it cannot be ruled out that the recombinant adenovirus can exchange its genetic material during co-infection of the same human cell by a wild-type adenovirus and thus reacquires a replication capacity generating RCA. The probability of occurrence of this event is extremely low and would involve only a limited number of viral particles which would be rapidly eliminated by the immune system, and consequently would have no effects on health of the persons in contact with the treated patient after a putative horizontal transmission.
- In addition, the respect of confinement, carrying out of protection, control and monitoring measures could reduce significantly the likelihood of post-release dissemination of the vector to other persons and since the presence of recombinant adenovirus has been demonstrated in body fluids, mainly within the 24 hours following administration, the treated patient should be hospitalised for 24 hours and visits should be restricted to health care workers who should avoid any direct contact with body fluids and secretions.

The experts estimate that with successive injections the risk of the patient to excrete virus particles will decrease. Patients who were already immunised against adenovirus will have had their immune system reactivated by the first injection. Patients who were not yet immunised against adenovirus will have their immunisation induced by the first injection and they will become each time more reactive against the viruses disseminated in their blood. Therefore taking into account the precaution principle, a 24 hours hospitalisation should be advised after the first injection of Ad-IL2. For the following injections, 6 to 8 hours hospitalisation should be enough to minimise the risk of post-release dissemination of the vector to other persons.

Conclusion

Based on the scientific assessment and knowing that, as stated in its advice of 26 March 2004, the risk of using this GMM in this clinical trial is, for human health and the environment, very low, the Biosafety Advisory Council considers that, without increasing the risk for human health and the environment, the condition 2 of its advice of 26 March 2004 can be restricted for each patient to the first injection of Ad-IL2. Therefore this condition can be interpreted in a less restrictive way and it becomes:

- After the first injection, the patients stays at least 24 hours in an individual room at the hospital until the level of viral vector in his body fluids has begun to decrease. For the following injections the length of the hospitalisation should be at least 6 hours in absence of any signs or symptoms of active concomitant respiratory tract infections.

The Biosafety Advisory Council has no comments about the new protocol amendment which has not any impact on the biosafety of the project.

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President of the Biosafety Advisory Council.

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