European Medicines Agency

London, 26 April 2007
Doc. Ref. EMEA/CHMP/GTWP/367513/2006

COMMITTEE FOR THE MEDICINAL PRODUCT FOR HUMAN USE (CHMP)

CONCEPT PAPER ON – The development of a Guideline on clinical monitoring and follow-up of patients exposed to gene therapy/gene transfer medicinal products.

AGREED BY GENE THERAPY WORKING PARTY	April 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	April 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	July 2007

Comments should be provided electronically in word format using this template to: GTWPsecretariat@emea.europa.eu

KEYWORDS	Gene therapy, clinical trial, follow-up, adverse events

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 16
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

INTRODUCTION

Gene therapy/transfer products for prevention, therapy or in vivo diagnosis of a variety of diseases have progressed from pre-clinical evaluation into clinical gene therapy studies in humans. The short-term risks resulting in expected or unexpected adverse reactions are normally detected within the time frame of the clinical trial due to the tight clinical control of the patient in this period. However, little information is gained about an eventual medium- or long-term risk of a given gene therapy medicinal product. By permanently altering the genetic makeup of the recipient cells, some forms of gene therapy may cause toxicities that do not reveal themselves until years later. Additionally, some gene therapies use viral vectors with the potential to form latent infections that may emerge clinically years later. Thus there is a need for a guideline for the long-term monitoring of delayed adverse events as a consequence of persistent biological activity of the genetic material or other components of the products used to carry the genetic material.

1. PROBLEM STATEMENT

The CPMP Note for guidance on the quality, pre-clinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99) describes the framework of technical requirements for marketing and, by discussing scientific principles, clinical testing of a gene therapy/transfer medicinal products. However, the Note for guidance only briefly comments on the short- to long-term patient safety and efficacy monitoring of the patient (see section "6.5. Patient monitoring" below).

"6.5. Patient monitoring

In view of the foregoing, the following aspects should be considered.

a) Short-term monitoring will cover human pharmacology (see section 6.2) and efficacy (see section 6.3) studies extensively. Safety studies will include issues relating to early toxicity whether general or organ-specific, virus-safety, immunotoxicity and elimination of gene transfer vector (see section 6.4 a, b, d and f).

b) Long-term monitoring encompasses
   (i) assessing for the gene expression and stability of the gene transfer procedure; and
   (ii) safety with particular emphasis on potential long term clinical consequences of gene integration and possible non-specific transduction of other cell types inherent in the vector employed, prolonged expression of a foreign protein and the use of viral vectors (see section 6.4 a, b, c and e).

The extent of data and the duration of monitoring should be justified by the applicant. The guidance of ICH E1 might not be relevant for this situation."

The Guideline on risk management systems for medicinal products for human use (EMEA/CHMP/96268/2005) provides guidance on how Marketing Authorisation Holders and Applicants should meet the requirements for a description of a risk management system they will introduce for an individual medicinal product and how a risk management system can be presented to Competent Authorities. Nevertheless, the Guideline on risk management systems for medicinal products for human use is not specific for certain medicinal products such as gene therapy/transfer products. The proposed guideline is aimed to provide key aspects for the risk management plan for gene therapy/transfer products and will give specific advice regarding the duration and the design of long-term follow up observations.

There is no recommendation on how to design or perform the long-term efficacy and safety follow-up of patients treated with gene therapy/transfer products with respect to the potential long-term clinical consequences of the duration and stability of gene expression, gene integration, a possible non-specific transduction of other cell types, prolonged expression of protein product and the use of viral vectors. There is also no recommendation under which circumstances a long-term follow-up of patients should be considered. Currently, there are no patient registries established across member states for the monitoring of long-term effects of gene therapy products.

In addition, there is no guidance on required evidence based information on how to properly investigate the potential risk for long-term adverse reactions of a gene transfer medicinal product before submitting an application for marketing approval.

DISCUSSION

Within the EU clinical trials with gene therapy/transfer medicinal products have been carried out for several years using many different gene therapy/transfer medicinal products. The clinical gene therapy trial approval is the responsibility of each EU member state (Directive 2001/20/EC). The requirements laid down in the Paediatric Regulation are also to be fulfilled. A harmonised approach on a European level is warranted.

The monitoring of the clinical trials during the initial treatment period and in the follow-up period is also the responsibility of each member state. The initial monitoring is described in the CPMP/BWP/3088/99 Note for guidance, but there is a lack of guidance for the long-term follow-up of the patients included in gene therapy/transfer trials. There is a need for establishing guidelines for the long-term follow-up of patients included in such trials. However, the required follow-up recommendations might vary depending on the gene therapy/transfer medicinal product, the transfer vector, the disease, concomitant diseases and patient age.

When gene therapy/transfer clinical trials are moving from the initial phase I to phase II and III they will often be conducted as multinational clinical trials. Both the clinical trial proposal and the monitoring plan are approved by the authorities in each member state in which the clinical trial is intended to be carried out.

The lack of recommendations for long-term follow-up of patients to whom gene therapy/transfer medicinal products have been administered results in a non-uniform follow-up of the patients in the individual member state, which is a potential safety problem for the patients, the pharmaceutical/biotechnology industry or for academic groups developing gene therapy/transfer products and the authorities in the individual member states.

There is a need for establishing a guideline with recommendations for the evaluation of the potential long-term risks of a gene transfer medicinal product, both when submitting an application for marketing authorisation and for the long-term follow-up of adverse events in patients included in gene therapy/transfer clinical trials.

2. RECOMMENDATION

The CHMP Gene Therapy Working Party proposes to draft a guideline on clinical monitoring and follow-up of patients to whom gene therapy/transfer medicinal products have been administered.
The guideline will give recommendations for the long-term follow-up of patients treated with gene therapy products to detect delayed adverse events and for the required information to set-up risk stratification for the marketing authorisation application. It will also make reference to public health issues related to transfer of vectors to contact persons of the patient.

Factors of importance that could be involved in a delayed adverse event will be addressed:

1. Persistence of the viral vector and the potential for latency followed by reactivation
2. Replication competence
3. Integration of genetic material into the host genome
4. Route and method of administration (that could influence the potential for integration)
5. Prolonged expression of the transgene
6. Altered expression of the host gene

The recommendations for long-term follow-up will take into consideration:

1. The transfer vector used (viral or non-viral vector)
2. Life span of target cells or tissues (e.g. stem cells with unlimited proliferative capacity vs irradiated cells)

3. The preclinical data for integration or persistence of vector sequences, latency, reactivation and duration of transgene expression
4. The expected survival rate of the clinical trial population
5. The prior, concomitant, and post gene therapy exposures of the study population to therapies or diseases which might influence the evaluation of the gene therapy
6. The prevalence of the disease for which an indication is thought
7. Other factors that may be of relevance for, or influence the scientific value of, long-term follow-up, i.e. concomitant medical treatment such as chemotherapy.

Recommendations will be given concerning principles (including key methodological aspects) of monitoring patients after finalisation of the clinical trial as well as after the marketing approval of the gene therapy/transfer medicinal product including:

1. methods to assess the risk of gene therapy-related delayed adverse reactions following administration of gene therapy products,
2. guidance to determine the likelihood that long-term follow-up observations on study participants will provide scientifically meaningful information,
3. key principles to be considered in the risk management plan, and
4. key principles to determine long-term efficacy.

3. PROPOSED TIMETABLE

It is anticipated that a draft guideline will be available 12 months after adoption of the concept paper and will be released for 6 months external consultation, before finalisation during the following 6 months.

4. RESOURCE REQUIREMENTS FOR PREPARATION

The guideline development will be led by the GTWP in collaboration with the Pharmacovigilance Working Party (PhVWP). Other relevant working parties, e.g. Safety Working Party (SWP), Cell-based Products Working Party (CPWP), Biologics Working Party (BWP) and Vaccine Working Party (VWP), as well as the Paediatric Committee will be consulted. In addition Working Groups with health care professionals and patient organisations will be contacted.
Drafting work will be conducted primarily by email and teleconferences. GTWP and PhVWP will discuss draft versions at their regular meetings. It is anticipated that at least two sessions of plenary GTWP-meetings in 2007 will be needed before the draft is finalised.

5. IMPACT ASSESSMENT (ANTICIPATED)

The guideline will provide assistance to applicants for clinical trials with gene therapy/transfer medicinal products, applicants submitting an application for marketing authorisation and to the member state competent authorities for planning, conducting, and evaluating the long-term follow-up of patients treated with gene therapy/transfer medicinal products. The recommendations in the guideline will result in a more uniform monitoring of patients treated with gene therapy/transfer medicinal products and, thereby, enhance the safety monitoring of the drug to the benefit for both the patients and the manufacturers of gene therapy/transfer medicinal products.

6. INTERESTED PARTIES

EMEA: Gene Therapy Working Party (GTWP), Pharmacovigilance Working Party (PhVWP), Safety Working Party (SWP), Cell-based Products Working Party (CPWP), Paediatric Committee, Biologics Working Party (BWP) and Vaccine Working Party (VWP).
External consultation: pharmaceutical industry, academic networks and learned societies within the EU.

7. REFERENCES TO LITERATURE, GUIDELINES ETC

The CPMP Note for guidance on the quality, pre-clinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99)
Clinical Trial Directive 2001/20/EC

Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 ("Paediatric regulation")