

ICH Considerations

Oncolytic Viruses November 13, 2008

1. Introduction

Oncolytic viruses (OV) were first observed in early clinical studies in patients with malignancies where tumour regressions were observed to coincide with viral infections or with live virus vaccinations. Since these early reports, studies using OV have progressed from anecdotal and controlled infections to specifically selecting or genetically modifying viruses for cancer treatment. OV are intended to propagate selectively in tumour tissue and spread, destroying the tissue without causing excessive damage to normal tissues.

OV can be wild type or naturally attenuated strains of viruses that possess an inherent property of selective replication and lysis of cancer cells. Additionally, viruses can be genetically modified to selectively replicate and lyse cancer cells. These modifications can include 1) the mutation of the viral coding genes that are critical for viral replication in normal cells, 2) the control of early gene expression by using tumour-specific promoters, 3) a change in the viral tissue tropism and/or cell entry process, and 4) the incorporation of transgenes into the viral genome. Examples of OV include adenovirus, measles virus, vesicular stomatitis virus (VSV), reovirus, Newcastle disease virus, herpes simplex (HSV), poxvirus, Sendai virus, and others.

Regulatory authorities represented at the ICH agree that the therapeutic potential of OV will need to be balanced against the risks associated with the use of virus that is replication competent. This document identifies general principles for the clinical development of OV regardless of the classification of such products in each region.

2. Product Characterization of Oncolytic Viruses

Manufacturing and characterization of OV follow the currently recognized principles for biologicals and, more specifically, for gene therapy products, as covered by regional guidelines. However, since the product is replication competent, there are specific technical challenges for adventitious agent testing and product characterization.

2.1 Selectivity

A clear understanding of the molecular basis for tumor selectivity is important. To demonstrate selectivity in tumour cells prior to use in human clinical studies, OV should be assayed *in vitro* for cytotoxicity/lysis and/or replication on permissive (tumour) and non-permissive (normal) cell lines. Primary explant cultures of normal and tumour-derived human tissues can also be used.

Tumour cell selectivity is not considered to be a direct measure of potency for this class of products. Release testing for potency should utilize assay(s) that measure or correlate with the biological activity of the OV, e.g., tumor cell lysis.

2.2 Molecular variants

For OV products, characterization includes testing the product for the presence of molecular variants of the intended oncolytic virus. A focus for testing should be potential variants that might have an altered replication selectivity or oncolytic profile. The testing strategy for

molecular variants may need to reflect both the nature and amount of the variant(s). Describing the history and selection procedures of OV can help in the demonstration and evaluation of genetic stability.

2.3 Adventitious agent testing

Adventitious agent testing can be particularly challenging for OV because these products can replicate in commonly used test systems, generating false positive results. One possible strategy to overcome this challenge is based on the use of specific antibodies to neutralize the OV prior to performing *in vivo* and *in vitro* adventitious agent testing. If a neutralizing antibody is not available then it might be appropriate to conduct adventitious agent testing on materials from parallel production cultures performed without the viral product, an approach similar to that used for testing live viral vaccines.

3. Non-clinical studies

Non-clinical studies should be conducted with the OV construct intended for use in clinical trials. It may be helpful to consider the results of studies conducted with viruses similar to the OV under investigation prior to initiating non-clinical studies.

3.1 Evaluation of Selectivity

Prior to using animal models, studies conducted *in vitro* to characterize selectivity in normal and tumour cells should address selective gene expression, cytotoxicity and viral replication (see Section 2.1).

When possible, selectivity of virus replication should also be studied using *in vivo* models (see Sections 3.3 – 3.6).

3.2 Selection and limitations of animal models

Selection of the animal model should take into consideration the purpose of the study as well as the viral tropism, infectivity, replication ability, cytopathic potential, and anti-tumour effect of the OV. Both non-tumour-bearing animal species and tumor-bearing xenograft or syngeneic animal models are useful for non-clinical testing, but the limiting factors include: species susceptibility to the viral infection and replication, and the inability to model all aspects of the immune response.

The permissiveness of the animal species to the parental virus of the OV needs to be considered. Standard animal species routinely used for non-clinical testing might not be appropriate; therefore, other animal species may need to be considered (e.g., cotton rats, Syrian hamsters). The species used should ideally be sensitive not just to infection by the virus, but also to the pathological consequences of infection that can be induced by the OV. In some cases, 'humanized' rodents can be used that express the human target receptor(s) either by genetic modification or cell / tissue transplantation.

Tumour-bearing models can be used to assess proof of concept (POC), pharmacokinetics, pharmacodynamics, viral shedding, and safety. Ideally, a xenograft or syngeneic model should represent the tumour biology and pathology of the target clinical population to the extent that therapeutic effectiveness observed in the animal model will be an indication of clinical outcome. This desired effect should be considered when evaluating the safety of the OV, as the level of viral presence and the extent of persistence in various biological samples of a tumour-bearing model can be significantly different than in a non-tumour-bearing animal.

However tumour-bearing models reflect only certain aspects of the tumour biology and pathology of the target clinical population. The limiting factors include, for example, when using a tumour xenograft model, the inability of an adenovirus to replicate in murine tissues;

this will limit the assessment of the replication effects of the virus. In addition the mouse host strains often used are immune deficient; therefore assessment of immune response to the OV will also be limited. One other potential disadvantage with the use of tumour-bearing models is that they have a reduced life span due to tumour growth. Therefore, the ability to assess long-term safety might be limited.

Non-tumour-bearing, biologically sensitive, animal species can be used to evaluate the safety of the OV to complement the information obtained from tumour-bearing models.

When the OV contains a transgene, it is important that the animal species be pharmacologically responsive to the expressed protein. If the expressed transgene is inactive in the animal species (e.g., human GM-CSF is inactive in mice), OV can be engineered to express the analogous species-specific transgene and used in non-clinical studies to assess both activity and safety. In these instances, characterization of the OV administered to animals should be performed to assess the extent of comparability to the intended clinical OV, e.g., level of transgene expression.

It is important to consider the intended clinical administration procedure for the OV when selecting the animal species. If the route is non-standard, such as intrahepatic arterial injection, a large animal species may be needed.

3.3 Pharmacology / POC

Aspects of biological activity such as POC and potential mechanism of action can be demonstrated using both *in vitro* and *in vivo* models. It is important to assess the bioactivity and pharmacologic profile of the OV to understand the ability of the OV to induce the desired biological effect(s) *in vivo*. Studies should contribute to establishment of the scientific justification for administration of the OV in a specified target population by addressing the biological feasibility of the use of the OV in the target cancer, including selectivity of replication and anti-tumor activity. In addition, non-clinical studies help to: 1) define a pharmacologically active dose range, with establishment of an optimal biological dose and a minimally effective dose, 2) determine a potentially optimal route for product administration, and 3) define a dosing schedule for early phase clinical trials.

3.4 Biodistribution

Biodistribution studies in animals address OV dissemination to target and non-target organs. OV dissemination can be detected using an assay for nucleic acid sequences. It is also recommended that testing for the presence of OV sequences in animal organs and tissues be done by at least one sensitive assay such as quantitative polymerase chain reaction (Q-PCR).

In parallel with determining the biodistribution profile of the viral genome is understanding the infectious potential of the administered OV. Viral titers and viral nucleic acid levels should be quantitated because OV are replication-competent and may have the potential to infect and replicate in normal tissues. The presence of viral genome sequences or transgene expression in non-target tissues at significant levels should trigger further analysis of the tissue/biological fluid. These data, coupled with toxicology study results, such as clinical pathology and histopathology evaluation, will determine whether virus presence and/or gene expression correlates with adverse safety signals in animals.

3.5 Viral Shedding Considerations

For the purposes of this ICH Considerations document, viral shedding is defined as the dissemination of the OV through excreta of the patient.

A concern in using OV is the potential to expose others. Assessment of viral shedding in animals will aid in the clinical monitoring plan. OV shedding information can be used to guide monitoring for long-term adverse effects in both non-clinical and clinical studies.

3.6 Toxicology and safety studies

The biodistribution and persistence profile of the OV and the expression profile of the transgene (if present) often guide the duration of the toxicology studies and the time intervals selected for sacrifice of animals. The toxicology assessment of an OV should be comprehensive enough to identify, characterize and quantify potential local and systemic toxicities following administration. The animal species, the route and procedure for product administration, the potentially therapeutic dose range and the dosing schedule, established from proof of concept studies, should guide the design of the toxicology studies. Since toxicity can be dependent on the route of administration of the OV, the route and the dosing schedule should mimic the intended clinical scenario as closely as possible. Outcomes measured include acute and chronic toxicities, reversibility of toxicities, delayed toxicities, and any dose-response effects. While certain aspects of the overall scientific principles of the ICH S6 guideline entitled, *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*¹, are applicable, the toxicology testing will need to reflect the biological characteristics of the OV, including the potential for viral replication and infectivity in normal cells/tissue and an undesired immune response to the virus and/or the expressed transgene.

3.7 Good Laboratory Practice (GLP) Studies

Safety endpoints are often collected in studies conducted using tumour-bearing animals, which can result in unique animal care situations. Full compliance with GLP, where required by regional law, can be difficult. Biosafety requirements can also impact the ability to conduct a non-clinical study with an OV in full compliance with GLP. Non-GLP studies might therefore be appropriate as long as they are performed in accordance with a prospectively designed protocol and the data are of sufficient quality and integrity to support the proposed clinical trial.

4. Clinical studies

Due to the complexity of OV products and the limited usefulness of animal models, many questions remain to be addressed in early phase clinical studies. This may introduce the need for caution in initial dosing regimens and routes of administration. Since animal dosing information may not provide adequate safety information there is still a need to perform dose ranging studies in cancer trial participants to determine a safe starting dose level. A strategy often used when determining appropriate route of administration has been to follow a stepwise approach starting with intratumoral injection, moving on to regional or local administration, and then to systemic administration. The selected route of administration should be justified and the potential replication of the virus in non-target sites should be considered.

When available, an antiviral therapy against undesired replication of OV or any molecular variants should be considered; e.g., gancyclovir could be useful to control replication of a HSV OV.

4.1 Pharmacokinetics, pharmacodynamics and biological activity

Both PCR and infectivity assays have been used for monitoring levels of OV. Monitoring should be performed in sufficient frequency and duration to detect a possible secondary peak of virus in the blood after administration, suggestive of viral replication in permissive tissues.

¹ICH S6 guideline entitled, *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*

Other approaches can be used to monitor the OV including the levels of any encoded viral marker or transgene expression.

Measuring presence and/or distribution of the OV within the tumour can be difficult but useful information can be provided from tumour pathology if resection or biopsy is possible.

4.2 Immunity and immune response

Pre-existing immunity (humoral and/or cellular) to the virus may influence the route of administration, the dosing regimen and the potential value of successive administrations. It is important to monitor for immune responses against the OV product (and, if present, any transgene product).

However, the impact of neutralizing anti-viral antibodies on efficacy is currently not understood. While this immunity is a potential safeguard against excessive viraemia, it might interfere with the goal of virus spread.

Consideration should also be given to the potential impact of inflammatory responses associated with the desired tumour cell lysis.

4.3 Biosafety

It is important that precautions for infectious material and biological safety, and biosafety guidelines or their equivalent, be followed when administering OV. Respective institutional, country, state, and local regulations should be followed. Generally, as part of the clinical protocol, all regulatory authorities require some form of barrier contraception for the duration of the clinical trial as a standard precaution.

Non-clinical viral shedding studies can be useful in preparing for clinical studies and evaluating detection methods. It is advisable to integrate monitoring for shed virus into the clinical development plan.

The consequences of transmission might not be well understood and precautions should be taken to minimize exposure of healthcare providers, family members, and other patient contacts. Extra consideration should be given to minimize the exposure of persons with suppressed or compromised immune systems as well as other relevant populations.

It may be appropriate to instruct the patient and family members in ways to minimise the exposure of others in transit following out-patient administration and in daily life. This may also include the advice to use specific sanitation measures. Many of these considerations might fall under the heading of environmental release/risk and regional authorities should be contacted for details.