Repeated dose toxicity and local tolerance study with recMAGE-A3+AS15 antigen specific cancer immunotherapeutic given intramuscularly to cynomolgus monkeys

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Abstract

The objective of this study was to evaluate the potential systemic and local effects induced by 25 repeated intramuscular injections of the full human dose (FHD) of recMAGE-A3+AS15 cancer immunotherapeutic (CI), and to evaluate their reversibility 3 months after the last injection. Cynomolgus was selected based on MAGE-A3 homology with humans. The CI was administered at 2-week intervals and combined with saline control group. A total of 5 males and 5 females were allocated to each group. At each time point, 3 males and 3 females were sacrificed and histological examinations were performed on all animals. The study was performed in compliance with Good Laboratory Practice and the CiToxLAB facility is AAALAC accredited.

Introduction

The recMAGE-A3/AS15 CI combination is under development as an antigen specific cancer immunotherapeutic (CI) for the treatment of non-small cell lung cancer and melanoma. The present study was conducted as part of the nonclinical safety package in support of the intended clinical development program. The objective of the study was to evaluate the potential systemic and local effects induced by 25 repeated intramuscular injections of the full human dose of recMAGE-A3+AS15 CI in the cynomolgus monkey, and to evaluate the reversibility of any effects 3 months after the last injection. The cynomolgus monkey was selected based on MAGE-A3 sequence homology with humans. AS15 is an immunostimulant that has been specifically selected to enhance the strength and duration of the immune response.

Materials and methods

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The study design is shown in Table 1. The control (saline) or test formulation (MAGE-A3/AS15) was administered by intramuscular injection every 2 weeks over a period of approximately 8 weeks, to a total of 25 injections. The last injection was administered on day 336. Principal animals from each group were sacrificed 3 days post last dose, and reversal animals were sacrificed 3 months after the last injection showing normal histological aspect of inguinal lymph nodes.

Conclusions

The potential systemic and local effects induced by 25 repeated intramuscular injections of the full human dose of recMAGE-A3+AS15 CI in the cynomolgus monkeys were evaluated, together with the reversibility of any effects 3 months after the last injection. Under the conditions of this study, 25 repeated injections of recMAGE-A3+AS15 CI were considered to be systemically and locally well tolerated by cynomolgus monkeys.

Figure 1: MAGE-A3 specific antibody response (Group 2; mean group values)

No toxicologically significant effects on clinical signs, body weight, body temperature (Table 2), electrocardiography, ophthalmology, hematology, clinical chemistry, organ weights or histopathology were observed.

Materials and methods

Groups

Table 2: Study design

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Groups

Results

Table 2: Body temperature (Group mean values)

Body temperature values for the cynomolgus monkey are variable, and are generally in the range 37.5 to 39.5°C.

Table 3: Circumference of injected limb (individual values in centimeters)

Immune responses elicited in the cynomolgus monkey were low to moderate in intensity. Injections were well tolerated in terms of systemic and local tolerance, and the safety profile of this vaccine was comparable to that of the lead clinical vaccine.

Figure 2: Selected clinical pathology parameters: neutrophils, monocytes, fibronectin

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Figure 4: Injection site histopathology

Principal animals sacrificed three months after the last injection showing normal histological aspect of skeletal muscle (Group 2 M: Male; Animal a04, b04; d04; e04).

Reversal animals sacrificed three months after the last injection showing normal histological aspect of skeletal muscle (Group 2 M: Male; Animal a04, b04; d04; e04).

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