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Evaluation of rabies immunogenicity and tolerability following a purified chick embryo cell rabies vaccine administered concomitantly with a Japanese encephalitis vaccine☆

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Abbreviations: GMC, geometric mean concentrations; JE, Japanese encephalitis; RVNA, rabies virus neutralizing antibody.

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Summary *Background:* For individuals traveling at short notice to rabies and Japanese encephalitis (JE) endemic countries, concomitant administration of travel vaccines within a short period is often required.
Methods: The aim of this study was to determine whether an accelerated (one-week: Days 1 −8) pre-exposure rabies (Rabipur®, Novartis Vaccines) vaccination regimen administered concomitantly with a Japanese encephalitis (JE) vaccination (Ixiaro®, Valneva) regimen, is non-inferior to the standard (four-week: Days 1, 8, 29) rabies regimen administered alone or concomitantly with the JE vaccine. Healthy adults (18 to ≤65 years) were randomized into Rabies + JE-Standard, Rabies + JE-Accelerated, Rabies-Standard and JE-Standard groups. Relative immunogenicity for rabies in each regimen was assessed using the rapid fluorescent focus inhibition test. Safety was evaluated up to and including Day 57.
Results: Non-inferior immunogenicity for rabies was established between the Rabies + JE-Accelerated group compared to both the Rabies-Standard and Rabies + JE-Standard groups; as well as between the Rabies + JE-Standard regimen and the Rabies-Standard regimen. By Day 57, adequate neutralizing levels were achieved by 97−100% of subjects across all groups. Adverse events (AEs) were comparable for all groups.
Conclusions: An accelerated pre-exposure rabies and JE vaccination regimen is non-inferior to the standard four-week rabies regimen and may thus provide a more convenient regimen for individuals traveling to endemic countries at short notice. NCT01662440.

1. Introduction

Rabies and Japanese encephalitis (JE) are serious diseases that are of concern to individuals traveling to countries where these conditions are prevalent. Prophylactic vaccinations against these diseases are thus recommended, particularly for prolonged trips and/or if access to medical care will be limited [1,2]. Rabies especially is a problem across large parts of Africa, India and Asia, where the incidence of injuries to travelers caused by potentially rabid animals is estimated to be approximately 0.4% per month of stay [3]. Pre-exposure rabies vaccination helps provide effective protection by inducing immunological memory. The regimen consists of three full intramuscular doses of a cell-culture based vaccine administered over a three to four week period [4].

The World Health Organization (WHO) International Travel and Health [4] recommends that travelers who are planning extensive outdoor exposure in endemic countries (e.g. camping, hiking etc.), particularly during the rainy season receive adequate immunization against JE prior to travel. Primary JE immunization consists of two intramuscular doses with an inactivated Vero cell-derived JE vaccine, administered four weeks apart [4]. In many countries in Asia, the risk of rabies and JE often overlap. Therefore, all travelers to these regions are advised to receive both a rabies and JE vaccination, regardless if they are traveling for leisure or business (including expatriates, military personnel and their families).

Despite such recommendations, a disproportionately low number of individuals seek out the rabies and/or JE vaccines prior to travel [5−9]. It has been suggested that the relatively long period needed to administer the current rabies and JE vaccinations (up to four weeks for both), may be a reason for the low vaccination rates [3,5,6,9]. For example, in a large survey of US travelers to Asia, a significant proportion stated that they were unable to receive a rabies vaccine due to insufficient time to complete the vaccination regimen prior to departure [6]. Furthermore, a European survey of 609 travelers found that of those who had consulted a travel clinic, over 40% visited the clinic four weeks or less prior to departure, and 20% had just planned their trip in the previous two weeks [10]. This suggests that shorter immunization regimens are needed by many travelers. Indeed, to encourage optimal protection, concomitant administration of multiple vaccines would be most convenient.

This study thus sought to determine the non-inferiority of immune responses to a rabies vaccine (Rabipur® Novartis Vaccines) administered concomitantly with a JE vaccine (Ixiaro®, Valneva), according to an accelerated (one-week) regimen, compared to the standard four-week rabies regimen. The immunogenicity against rabies following concomitant administration of the two vaccines according to the standard four-week regimen was also evaluated, in addition to the tolerability of all vaccine combinations. Short-term immunogenicity and safety up to Day 57 are presented.

2. Methods

2.1. Study design

This Phase IIIb randomized, observer-blind, multi-center study was conducted at seven centers in Austria, Germany and Switzerland (NCT01662440). The study was undertaken in compliance with Good Clinical Practice and the Declaration of Helsinki (version 2008). Ethics review committees of participating centers approved the protocol and its