

COMPOSITIONS AND METHODS

FIELD OF THE INVENTION

5 The invention relates to compositions useful in inducing immune responses against Varicella-Zoster Virus (VZV). In particular the invention relates to viral vectors comprising epitope(s) from VZV Gly E protein, such as adenoviral vectors comprising same.

10 BACKGROUND TO THE INVENTION

Varicella-zoster virus (VZV or “Zoster Virus”) causes chicken pox, mainly in children. However, more importantly, the same virus can re-emerge in adults, usually decades after the primary chickenpox infection, causing the serious disease shingles.

15 Shingles, also known as herpes zoster, is an infection of a nerve and the skin around it. According to the NHS (the U.K.’s National Health Service), it is estimated that approximately one in every four people will have at least one episode of shingles during their life.

20 The main symptom of shingles is pain, followed by a rash that develops into itchy blisters, similar in appearance to chickenpox. New blisters may appear for up to a week, but a few days after appearing they become yellowish in colour, flatten and dry out. Scabs then form where the blisters were, which may leave some slight scarring and
25 loss of skin pigment. The pain may be a constant, dull or burning sensation, and its intensity can vary from mild to severe. Patients may have sharp stabbing pains from time to time, and the affected area of skin will usually be tender. In some cases shingles may cause some early symptoms that develop a few days before the painful rash first appears, such as a headache, burning, tingling, numbness or itchiness of the skin in the
30 affected area, a feeling of being generally unwell, and/or a high temperature (fever).

An episode of shingles typically lasts around two to four weeks. It usually affects a specific area on just one side of the body. It doesn't usually cross over the midline of the body. Any part of your body can be affected, including the face and eyes, but the
35 chest and abdomen are the most common areas.

With life expectancy in the UK now above eighty years of age, long term health maintenance is a key aim of modern healthcare. Medical developments which specifically target impactful illnesses occurring more frequently in the older adult, such as shingles, will play a critical role in lowering the burden of disease and associated healthcare demands.

More than 90% of adults have been infected with varicella-zoster virus (VZV) and therefore are at risk of developing shingles (herpes zoster). Although shingles is most frequent in older adults (> 50 years of age), it can occur at any age and especially in people who are immune-compromised (have a weakened immune system). Normally, the immune system can control the virus, but later in life VZV can be reactivated and result in shingles. It is not clear why this may happen but it could be linked to immunosenescence (a gradual deterioration of the immune system brought on by aging). The development of vaccines that specifically protect against illnesses that target the older adult is a key healthcare initiative.

It is desirable to reduce the severity of symptoms and/or the risk of developing complications. Complications of shingles can include meningitis or encephalitis; if shingles affects the eye(s) there is a risk of developing permanent vision problems if the condition isn't treated quickly.

EP3210631 discloses a DNA vaccine composition for preventing and treating herpes zoster, and method for activating T cells for VZV antigen by using same. This document describes a DNA vaccine composition for preventing and treating herpes zoster, containing: at least one type of plasmid containing the insertion site of a varicella-zoster virus (VZV)-derived gene encoding a VZV protein; and other pharmaceutically acceptable ingredients. There is no mention of viral vectors in this document.

WO2014/043189 discloses conditionally replication deficient herpes viruses and use thereof in vaccines. Creation of variant or mutagenised herpes viruses and host cells containing rendered conditionally replication defective by the incorporation or fusion of one or more destabilization domains onto one or more genes which are essential for viral replication are described. There is no mention of viral vectors in this document.

EP1721981 discloses recombinant varicella-zoster virus prepared using BAC (*E. coli* artificial chromosome), and a pharmaceutical composition comprising such a virus.

The focus of this document is on identification of non-essential regions in the VZV, in particular wherein the non-essential region is the region flanking the ORF of gene 11, or the region flanking the ORF of gene 12. There is no mention of viral vectors carrying VZV antigen(s) in this document.

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WO2009/012486 discloses varicella zoster virus-virus like particles (VLPS) and antigens. In particular this document describes a purified virus like particle (VLP) from Varicella Zoster Virus (VZV) comprising VZV gE protein, but does not include VZV nucleic acid or a yeast Ty protein. The focus of this document is on VLPs further comprising at least one additional protein from an infectious agent. The only mention of viral vectors in this document is in paragraphs 0048-0049 as general expression vectors.

Prior art vaccines against this virus include Zostavax™ (made by Merck). The protection from Zostavax™ is mainly via the antibody response. The European Medicines Agency (EMA) document WC500053460 discusses Zostavax, and it is asserted in the art that the correlation between immune responses and protection against Herpes Zoster (HZ) were observed with gpELISA measurements, while, the results of VZV IFN-γ ELISPOT test had a less clear correlation to the protection. Zostavax™ is typically given in the UK to all adults at age 70. However, the vaccine is not fully effective, and its usefulness against shingles decreases with age (from 69.8% in adults between the ages of 50-59 years, to 37.6% in those ≥70 years of age). Thus the efficacy is 30-40% which is very poor. This is a problem in the art. In addition, the protection given by Zostavax™ is typically 5 years or less, which is problematically short.

Furthermore, the vaccine is not recommended for people with weakened immune systems who are at an increased risk of developing shingles (e.g. patients with HIV). There is, therefore, an unmet need for a vaccine that gives improved protection across all ages, but especially in elderly and immunocompromised populations.

Zostavax™ is a live attenuated virus. Therefore, when given to humans, it causes a limited infection which boosts the immune response in humans without causing the shingles disease. It should be noted that this preparation does not replicate in mice, so when given to mice it is more similar to giving a replication defective virus.

SHINGRIX™ is a vaccine indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older. SHINGRIX™ is manufactured by GlaxoSmithKline Biologicals, Rixensart, Belgium. SHINGRIX™ is prepared by reconstituting a lyophilized varicella zoster virus glycoprotein E (gE) antigen component with an accompanying AS01B adjuvant suspension component. Thus, SHINGRIX™ is a protein vaccine based on the Gly E antigen. This has to be given as 2 administrations in order to be effective. Each administration has to be given with an adjuvant such as the AS01 adjuvant. This adjuvant is a reactogenic, which can be uncomfortable for patients - 85% of recipients report pain on injection. Side effects of SHINGRIX™ which may occur include redness, itching, swelling, warmth, bruising, or pain at the injection site. Headache, muscle pain, tiredness, or fever may also occur. Moreover, the reactogenicity can cause a secondary problem of compliance. This is because the reaction experienced after administering the vaccine tends to put patients off from returning for their second dose, yet the second dose is needed in order to complete the recommended regimen and associated level of protection. This is a problem in the art.

A further drawback with prior art approaches such as the SHINGRIX™ vaccine is that it requires two vials of material to be stored and mixed at the point of administration – in the case of SHINGRIX™ this is a vial of adjuvant and a vial of antigen which are formulated into a single mixture at the point of administration.

In the US, the list price for Zostavax is \$196.91 per dose in the private sector and \$117.12 per dose for CDC vaccine contracts. In terms of reimbursement, Zostavax is covered by most private health insurers in the US (98%) for adults age ≥60 years (although some plans may require patient co-pay). The vaccine is also covered by Medicare for adults aged ≥65 years, although it would be under Part D (which often has co-pay requirements and out-of-pocket expenses). Moreover, commentators identify Shingrix's 2-dose administration and its tolerability profile to be potential weaknesses. Thus there are persisting problems with prior art approaches.

The invention seeks to overcome problem(s) associated with the prior art.

SUMMARY OF THE INVENTION

Lack of adequate cell-mediated immunity (CMI) to varicella-zoster virus (VZV) has been associated with higher risks of developing shingles and associated pain.

The invention describes an adenovirus – Gly E zoster virus vaccine. It is shown to induce a T-cell response. These vectors can be used in prime boost vaccination regimes. A strong T-cell response is demonstrated by data provided in this application. Thus, the invention provides an advantageous, strong and maintained T-cell response.

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Varicella zoster virus (VZV) causes chickenpox and Zoster (shingles). Chickenpox is a highly contagious disease caused by the initial infection with varicella zoster virus (VZV). Chickenpox is one of the most common childhood diseases and is characterised by a blister-like rash and fever, with more than 90% of the population being exposed during the first two decades of life. Although chickenpox is generally a mild self-limiting illness, in immunocompromised subjects and adults it can be more serious. Zoster or shingles is caused by the reactivation of VZV persisting in a latent form in the dorsal sensory ganglia. Prevention of chickenpox through vaccination is a desirable medicinal intervention.

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It should be noted that the compositions and/or vaccines described herein are not therapeutic i.e. they are not taught as eliminating/eradicating virus. They are taught as vaccine compositions for use in maintaining control of VZV infection(s) and/or preventing resurgence of replicative VZV infection causing shingles. In other words, the compositions are taught as vaccine compositions for use in induction of immune responses from the host organism, not as agents directly acting on the virus itself. The compositions are useful to induce protection against an initial infection as in chickenpox, and/or to induce protection against reactivation of a latent virus (sometimes called ‘dormant virus’) as in shingles.

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Suitably references to ‘existing infection’ mean ‘latent infection’ or ‘static infection’ i.e. virus in the lysogenic phase of the lifecycle i.e. a dormant VZV infection (defined as one that is no longer causing an active infection).

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Suitably references to ‘infection’ have their normal meaning in the art, i.e. active infection or productive virus infection causing disease such as chickenpox or shingles, most suitably shingles. ‘Infection’ would normally have associated viraemia i.e. active infection (rather than latent infection as discussed above).

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Suitably the compositions described herein are for use in prevention of resurgent VZV infection, suitably for use in prevention of replicative VZV infection, suitably for use in prevention of disease(s) caused by reactivation of latent VZV infection.

Without wishing to be bound by theory, the inventors believe that the resurgence of the virus in adults causing shingles can be because of waning T-cell responses/waning number of T-cells against the virus in circulation. For this reason, the inventors teach
5 for the first time that existing approaches (which are based mainly on the antibody response) may not be fit for purpose. For these reasons, the inventors teach the viral vectored constructs as set out in the claims which have the advantage of inducing strong cellular immune responses, for example T-cell responses, and thereby protecting the recipients.

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In a broad aspect, the invention relates to a viral vector comprising nucleic acid having a polynucleotide sequence encoding at least one epitope of the varicella-zoster virus (VZV) Gly E antigen. Suitably the viral vector and the varicella-zoster virus (VZV) Gly E antigen are heterologous i.e. suitably the viral vector is not, or is not derived from,
15 VZV.

Suitably the invention relates to a viral vector comprising nucleic acid having a polynucleotide sequence encoding at least one epitope of the varicella-zoster virus (VZV) Gly E antigen, wherein said viral vector is an adenoviral vector.

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In one aspect, the invention relates to a composition comprising a viral vector comprising nucleic acid having a polynucleotide sequence encoding at least one epitope of the varicella-zoster virus (VZV) Gly E antigen, wherein said viral vector is an adenoviral vector.

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Suitably said at least one epitope comprises at least one CD4 T cell epitope and at least one CD8 T cell epitope.

Suitably said adenoviral vector is of human or simian origin.

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Suitably said adenoviral vector is ChAdOx 1 or ChAdOx 2.

Suitably said composition is adjuvant-free.

35 Suitably said Gly E antigen has the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2, suitably SEQ ID NO: 2.

Suitably said polynucleotide sequence comprises the sequence of SEQ ID NO: 3 or SEQ ID NO: 4, suitably SEQ ID NO: 4.

5 Suitably said polynucleotide sequence further comprises the sequence of the bgh polyadenylation signal SEQ ID NO: 6.

Suitably said polynucleotide sequence encoding at least one epitope of the varicella-zoster virus (VZV) Gly E antigen is operably connected to the long CMV promoter, suitably the long CMV promoter has the nucleotide sequence of SEQ ID NO: 7.

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Suitably said viral vector sequence is as in ECACC accession number 12052403 (ChAdOx1).

15 Suitably said viral vector sequence is as in SEQ ID NO: 5 (ChAdOx2).

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Suitably administration of a single dose of said composition to a mammalian subject induces protective immunity in said subject.

Suitably the composition as described above is formulated such that administration of a single dose of said composition to a mammalian subject induces protective immunity in
20 said subject.

Suitably the composition as described above is for induction of an immune response against VZV.

25 Suitably said immune response is a cellular immune response. Suitably said cellular immune response comprises a NK cell response and/or a T cell response. Suitably said cellular immune response comprises a T cell response. Suitably said T cell response comprises a CD8+ T cell response. Suitably said T cell response comprises a CD4+ T cell response. More suitably said T cell response comprises a CD8+ and a CD4+ T cell
30 response. Most suitably said T cell response comprises a CD4+ T cell response. Suitably said T cell response comprises a triple secreting CD4+ T cell response.

Suitably the composition as described above is for induction of an immune response against VZV, wherein a single dose of said composition is administered.

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Suitably the composition as described above is for induction of an immune response against VZV, wherein said composition is administered once.

The invention advantageously provides a composition which has the advantage of being effective when administered only once. However, in one embodiment, if the immune response in a subject wanes over time then suitably the composition may be
5 administered (readministered) to said subject. For example, said composition may be administered every 5 years, more suitably once every year.

Suitably the composition as described above is for induction of an immune response against VZV, wherein said composition is administered once per 5 years, more suitably
10 once per year.

Suitably the composition as described above is for preventing VZV infection.

Suitably the composition as described above is for prevention of shingles.
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Suitably the composition as described above is for preventing VZV infection, or for prevention of shingles, wherein a single dose of said composition is administered.

Suitably the composition as described above is for preventing VZV infection, or for
20 prevention of shingles, wherein said composition is administered once.

Suitably the composition as described above is for use in preventing VZV infection.

Suitably the composition as described above is for use in prevention of shingles.
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Suitably the composition as described above is for use in preventing VZV infection, or for use in prevention of shingles, wherein a single dose of said composition is administered.

Suitably the composition as described above is for use in preventing VZV infection, or
30 for use in prevention of shingles, wherein said composition is administered once.

In one aspect, the invention relates to use of a composition as described above in medicine.
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In one aspect, the invention relates to use of a composition as described above in the preparation of a medicament for prevention of VZV infection.

In one aspect, the invention relates to use of a composition as described above in the preparation of a medicament for prevention of shingles.

5 In one aspect, the invention relates to use of a composition as described above in the preparation of a medicament for induction of, or that induces, both CD4+ and CD8+ T cell responses to Gly E antigen in a subject. Suitably said medicament further induces antibodies to Gly E antigen in said subject.

10 In one aspect, the invention relates to a method of inducing an immune response against varicella-zoster virus (VZV) in a mammalian subject, the method comprising administering a composition as described above to said subject.

In one aspect, the invention relates to a method of preventing shingles in a mammalian
15 subject, the method comprising administering a composition as described above to said subject.

Suitably a single dose of said composition is administered to said subject.

Suitably said composition is administered once.

20 Suitably said composition is administered once per 5 years, more suitably once per year.

Suitably said composition is administered by a route of administration selected from a group consisting of subcutaneous, intradermal and intramuscular. Suitably said
25 administration is intramuscular.

In one embodiment suitably the composition as described above is for treatment or prevention of chickenpox.

30 DETAILED DESCRIPTION OF THE INVENTION

The inventors have used an innovative technology, viral vectored vaccines to protect against infectious disease. The inventors use their approach to 're-purpose' a virus by inserting a small part of a different virus (the one that causes the target disease) into a
35 virus vectored backbone. These 'recombined' viral vaccines can't replicate and will not cause disease - but can induce a strong immune response toward the inserted or foreign virus segment. The inventors have demonstrated that viral vectored vaccines are safe

and can effectively induce an immune response in the older adult and in immune-compromised individuals (HIV infected) - both key populations at risk of developing shingles.

Here we teach viral vectored vaccines toward VZV (the underlying causative agent in shingles) and we test these vaccines and show that they can induce an immune response in appropriate models.

In the art, recent data suggest that a newly developed vaccine (Shingrix™ - adjuvanted protein) toward shingles can induce protective efficacy toward shingles, if given as repeated immunizations. Unfortunately, the main use of adjuvants (i.e. to induce strong immune responses) can as a corollary induce adverse reactions, which is a problem in the art. Advantageously, whilst viral vectored vaccines of the invention can induce similarly strong immune responses, limited or minimal adverse reactions are seen post-vaccination.

We have generated viral vectored vaccines toward VZV tested that these vaccines can induce an immune response in appropriate models.

We teach various vaccination regimens to induce strong and long-lived immunity toward VZV.

We have generated VZV-vaccines and vaccination studies have demonstrated stronger cell-mediated immunity (CMI) than that achieved with the current licensed vaccine known in the art.

As used herein, the term 'about' means +/- 1% of the value given.

The invention provides vectors (suitably viral vectors, most suitably adenoviral vectors), compositions and formulations (such as pharmaceutical compositions, such as medicaments, such as vaccines) suitable for inducing an immune response, suitably a T cell mediated immune response, against a varicella zoster virus (VZV) in a vertebrate subject (suitably a mammal, more suitably a primate, most suitably a human).

Suitably the immune response comprises a cell mediated response.

Suitably the immune response comprises cell mediated immunity (CMI).

Suitably the immune response comprises induction of CD4+ T cells.

Suitably the immune response comprises induction of a CD4+ cytotoxic T cell (CTL) response.

In one embodiment the immune response comprises both a humoral response and a cell mediated response.

Suitably the immune response comprises protective immunity.

Suitably vector(s) of the invention comprise nucleic acid having polynucleotide sequence encoding one or more epitopes of the antigen of interest. In one embodiment
5 suitably vector(s) of the invention comprise nucleic acid having polynucleotide sequence which is the complement of nucleotide sequence encoding one or more epitopes of the antigen of interest.

Suitably the one or more epitope(s) is/are T cell epitope(s). Suitably the one or more
10 epitope(s) is/are CD4+ T cell epitope(s). Suitably the one or more epitope(s) is/are CD8+ T cell epitope(s). Suitably the one or more epitope(s) comprise at least one CD4+ T cell epitope and at least one CD8+ T cell epitope.

Suitably vector(s) of the invention comprise nucleic acid having polynucleotide
15 sequence encoding CD4 T cell epitopes of GlyE.

Suitably vector(s) of the invention comprise nucleic acid having polynucleotide sequence encoding CD8 T cell epitopes of GlyE.

Suitably vector(s) of the invention comprise nucleic acid having polynucleotide sequence encoding both CD4 and CD8 T cell epitopes of GlyE.
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Suitably the vector is used to induce both CD4 and CD8 T cell responses to GlyE (especially in humans); most suitably to induce both CD4 and CD8 T cell responses to GlyE (especially in humans) in addition to antibodies.

This further distinguishes the ChAd vaccines of the invention from prior art such as
25 Shingrix. Moreover this shows another property of the invention that is distinctive and improved over the prior art.

Adenoviral vectors have DNA genomes. Thus the nucleic acid is suitably DNA, most suitably dsDNA.

30 Suitably the adenoviral vector is of simian or human origin; suitably the adenoviral vector is of chimpanzee or human origin; suitably the adenoviral vector is of chimpanzee origin.

Suitably the nucleotide sequence is DNA sequence.

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In one embodiment we provide one of the main VZV surface antigens, glycoprotein E, cloned into a ChAdOx1 viral vector backbone. Expression is driven by the long CMV

promoter. The use of chimp-derived viral vectored vaccines to augment immune responses toward VZV gpE has not been done before, to the best of the inventors' knowledge. Critically, we have also demonstrated that viral vectored vaccines are safe and can effectively induce an immune response in the older adult and in immune-
5 compromised individuals (HIV infected) - both key populations at risk of developing shingles.

SHINGLES (HERPES ZOSTER) AND CHICKENPOX (VARICELLA)

10 As noted above, shingles (sometimes referred to as 'Herpes Zoster') is caused by varicella zoster virus (VZV), the same virus that causes chickenpox. Most people have chickenpox in childhood, but after the illness has resolved the varicella-zoster virus remains inactive (dormant) in the nervous system. The immune system keeps the virus in check, but the VZV can be reactivated later in life and cause shingles.

15 Without wishing to be bound by theory, it is not well understood why the shingles virus is reactivated at a later stage in life, but most cases are thought to be caused by having lowered immunity.

20 In more detail, infection with varicella-zoster virus (VZV), an alpha herpesvirus, is associated with two distinct diseases; varicella and herpes zoster. Primary infection results in chickenpox (varicella) a generally mild, self-limiting illness usually acquired in childhood or adolescence and affecting almost all individuals. Following initial primary infection with VZV, the virus remains latent in the dorsal root ganglia. It is
25 assumed that latent virus may frequently reactivate and replicate subclinically. These episodes of transient subclinical viremia lead to repeated antigenic stimulation of immunity without clinical manifestations of disease. In some individuals, however, reactivation and replication of the latent virus result in the clinical manifestation of herpes zoster (HZ), which is often referred to as shingles. HZ is characterized by a
30 unilateral, vesicular rash with a dermatomal distribution that generally corresponds to the area of skin innervated by a single spinal or cranial sensory ganglion. Typically, the vesicles crust over in 7 to 10 days, but may take up to a month to heal. One of the most significant clinical manifestations of HZ is pain, which is considered to be due to VZV induced neuronal destruction and inflammation. HZ-related pain may occur during 3
35 time periods: - prior to onset of the cutaneous eruption (prodromal pain, typically beginning 3 to 5 days prior to the appearance of skin lesions): - during the period of the acute rash (acute neuritis), and following healing of the acute skin lesions; - beyond

- cutaneous healing for a prolonged period of time (postherpetic neuralgia, PHN). PHN, the most severe sequelae of HZ, occurs in 10-20% of HZ patients and is described by characteristic patterns of pain with the majority of patients experiencing the following patterns - constant pain described as burning, throbbing or aching pain; - intermittent sharp, stabbing, shooting, lancinating pain; - stimulus-evoked pain as allodynia that usually lasts well beyond the duration of the stimulus. Allodynia, which is present in at least 90% of PHN patients, is typically described as the most distressing and debilitating component of HZ.
- 10 The mechanisms leading to HZ are not well understood, however, one predisposing factor in developing HZ in immunocompetent persons is advancing age. The incidence and severity of HZ increase from 2.5 per 1000 person-years in adults aged 20–50 years to 7.8 per 1000 person-years in those aged >60 years. Furthermore, complications such as PHN, which are relatively infrequent in otherwise healthy children and younger adults, occur in almost one-half of older individuals. It is postulated that the age-related increase in the risk of HZ among otherwise healthy elderly subjects is attributed to immunosenescence and has been correlated with a diminished cell-mediated immunity (CMI), but not with the level of circulating VZV specific serum antibodies. However, studies conducted in immunocompromised patients indicate, that low or absent CMI represents a necessary, but not a sufficient condition for the occurrence of HZ.

VIRAL VECTORS

- 25 Suitably the viral vector (sometimes referred to as ‘vector’) is an adenoviral vector.
- Suitably said coding sequence is present in an adenovirus based vector. In other words, suitably said coding sequence is present in an adenoviral vector.
- Any suitable adeno-based viral vector may be used.
- 30 The adenoviral vector of the invention may be any adenoviral vector suitable for use in humans.
- In more detail, any replication-deficient viral vector, for human use preferably derived from a non-human adenovirus may be used. For veterinary use Ad5 may be used.
- 35 Suitably the vector may be ChAdOx1.
- Suitably the vector may be ChAdOx2.

ChAdOx1

ChAdOx1 is described in patent application number WO2012/172277. In brief ChAdOx1 is derived from the "Y25" chimpanzee adenovirus isolate. A replication deficient vector derived from Y25 was taken and the E1 and E3 genes were deleted. In order to improve yields, some ORFs in E4 were replaced with the corresponding ORFs from human adenovirus 5 (three such ORFs were replaced) which lead to better yields. E4 is involved with viral replication and is not believed to affect immunogenicity/safety.

In more detail, ChAdOx1 is described in Dicks MDJ, Spencer AJ, Edwards NJ, Wadell G, Bojang K, et al. (2012) A Novel Chimpanzee Adenovirus Vector with Low Human Seroprevalence: Improved Systems for Vector Derivation and Comparative Immunogenicity. PLoS ONE 7(7): e40385, and in WO2012/172277. Both these documents are hereby incorporated herein by reference, in particular for the specific teachings of the ChAdOx1 vector, including its construction and manufacture.

In addition, a clone of ChAdOx1 containing GFP is deposited with the ECACC: a sample of *E. coli* strain SW1029 (a derivative of DH10B) containing bacterial artificial chromosomes (BACs) containing the cloned genome of AdChOX1 (pBACe3.6 AdChOx1 (E4 modified) TlPeGFP, cell line name "AdChOx1 (E4 modified) TlPeGFP") was deposited by Isis Innovation Limited on 24 May 2012 with the European Collection of Cell Cultures (ECACC) at the Health Protection Agency Culture Collections, Health Protection Agency, Porton Down, Salisbury SP4 0JG, United Kingdom under the Budapest Treaty and designated by provisional accession no. 12052403. Isis Innovation Limited is the former name of the proprietor/applicant of this patent/application.

ChAdOx2

ChAdOx2 is described in patent application WO2017/221031. Similar to ChAdOx1, ChAdOx2 is derived from a C68 isolate of chimpanzee adenovirus. Again a replication defective virus was obtained and the E1 and E3 genes were deleted. The replacement of three E4 ORFs as conducted on ChAdOx1 presented challenges when implemented on ChAdOx2. Therefore, the whole E4 region of ChAdOx2 was replaced with the engineered E4 region of ChAdOx1 (as described above).

In more detail, The nucleotide sequence of the ChAdOx2 vector (with a Gateway™ cassette in the E1 locus) is shown in SEQ ID NO. 5 This is a viral vector based on

Chimpanzee adenovirus C68. (This is the sequence of SEQ ID NO: 10 in GB patent application number 1610967.0 - the priority application for WO2017/221031).

5 In addition, a clone of ChAdOx2 containing GFP is deposited with the ECACC: deposit accession number 16061301 was deposited by Isis Innovation Limited on 13 June 2016 with the European Collection of Cell Cultures (ECACC) at the Health Protection Agency Culture Collections, Health Protection Agency, Porton Down, Salisbury SP4 0JG, United Kingdom under the Budapest Treaty. Isis Innovation Limited is the former name of the proprietor/applicant of this patent/application.

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Therefore, because ChAdOx1 and ChAdOx2 are different to some degree, they can be used together in heterologous prime boost regimes (e.g. a ChAdOx1 prime followed by a ChAdOx2 boost, or a ChAdOx2 prime followed by a ChAdOx1 boost). Of course, either of these vectors may be used in conventional heterologous prime boost regimes for
15 example adenovirus prime followed by pox virus boost, or pox virus prime followed by adenovirus boost.

Manufacture of vaccine doses from ChAdOx1/ChAdOx2 is identical. Therefore, techniques described herein for manipulation/amplification/preparation of ChAdOx
20 vectors may apply equally to ChAdOx1 and/or ChAdOx2.

Whilst the general principles of manufacture are identical, there will be some minor differences in the exact conditions for downstream processing due to slightly different charge on the virions. This is well within routine variations for a person skilled in the art of virus production.

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In brief, manufacture/harvest/purification of viral vectors for compositions of the invention is suitably carried out under GMP (Good Manufacturing Practice) conditions. The viral vectors of the present invention may be produced in engineered cell lines containing a complement of any deleted genes required for viral replication. The
30 adenoviral vectors according to the present invention suitably further comprise one or more modifications designed to optimise vector growth and yield in transformed cell lines, such as HEK293, expressing the genes functionally deleted in the adenoviral vector according to the present invention. Manufacture of adenoviral vectors is well known in the art. In particular, precise conditions for production of adenoviral vectors
35 such as the ChAdOx1 and ChAdOx2 vectors, are described in prior art such as WO2012/172277 or WO2017/221031.

FORMULATION

The formulation buffer, as used for the clinical product is:

5 Formulation Buffer Components

1. 10 mM Histidine
2. 7.5 % Sucrose
3. 35 mM Sodium chloride
- 10 4. 1 mM Magnesium chloride
5. 0.1 % Polysorbate 80
6. 0.1 mM EDTA
7. 0.5% Ethanol
8. Hydrochloric acid (for pH adjustment to ~pH 6.6)
- 15 Formulated in water for injection Ph Eur.

Other formulations may be used, for example Alternative buffer e.g. Merck Formulation Buffer A195 (10mM Tris, 10mM Histidine, 5% sucrose, 75mM NaCl, 1mM MgCl₂, 0.02% PS-80, 0.1mM EDTA, 0.5% EtOH, pH 7.4).

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Formulations for other administration routes such as aerosol will be adjusted accordingly by the skilled operator.

Suitably the composition and/or formulation does not comprise adjuvant. Suitably
25 adjuvant is omitted from the composition and/or formulation of the invention.

Antigen Insertion

For insertion of the nucleotide sequence encoding Gly E antigen, suitably the E1 site may be used, suitably with the hCMV IE promoter. Insertion into the E1 site is well
30 within the ambit of the skilled reader; in the event that any guidance was needed reference is made to the description of the ChAdOx1 and ChAdOx2 vectors (see above), and/or to WO2012/172277 or WO2017/221031. Suitably the short or the long version of the hCMV IE promoter may be used; most suitably the long version as described in WO2008/122811, which is specifically incorporated herein by reference for the
35 teaching of the promoters, particularly the long promoter.

It is also possible to insert antigens at the E3 site, or close to the inverted terminal repeat sequences, if desired.

ANTIGEN EXPRESSION

Antigen may be constitutively expressed from viral vectors. Indeed, the inventors have
5 shown that viral vectors described herein constitutively expressing the antigen are
stable through numerous passages. This is an advantage of the invention. However, if
desired, the expression of the antigen may be repressed during manufacture which may
lead to better yields and/or may avoid problems with antigen toxicity. This is a matter
for operator choice.

10

Data presented herein includes ELISPOT data showing T-cell responses. This is a
departure from prior art approaches where zoster virus vaccines have been primarily
focussed on the antibody response.

15 VARICELLA-ZOSTER VIRUS (VZV)

In another aspect, the invention relates to a vector, composition or medicament as
described herein for treatment of VZV infection. By 'treatment' is meant control or
prevention of resurgence e.g. from dormant virus (sometimes referred to as
20 'endogenous virus' in mammals such as primates e.g. humans).

Suitably the vector, composition or medicament of the invention is for controlling
reactivation of VZV.

25 Suitably the vector, composition or medicament is for preventing resurgence of VZV
infection.

Suitably the vector, composition or medicament is for controlling shingles.

30 Suitably the vector, composition or medicament is for preventing shingles.

ADVANTAGES

A drawback with prior art approaches such as the SHINGRIX™ vaccine is that it
35 requires two vials of material to be stored and mixed at the point of administration – in
the case of SHINGRIX™ this is a vial of adjuvant and a vial of antigen which are
formulated into a single mixture at the point of administration. In contrast, the present

invention advantageously requires only a single vial of material to be stored/
transported/ manipulated.

Furthermore, it is an advantage of the invention that superior immunogenicity is
5 delivered compared to either Zostavax or SHINGRIX™ prior art vaccines.

It is an advantage of the invention that only a single dose is needed.

It is an advantage of the invention that only a single dose is needed to induce an
10 immune response.

It is an advantage of the invention that the vectors are safe in immune compromised
subjects.

15 It is an advantage of the invention that a better response is observed compared to prior
art approaches.

It is an advantage of the invention that T-cell responses are generated, in particular
CD4+ T-cell responses.
20

In some embodiments it is an advantage of the invention that CD8+ T-cell responses
are also generated; in some embodiments it is an advantage of the invention that strong
antibody responses are also generated; most importantly the invention provides the
advantage of generating / enhancing CD4+ T-cell responses.
25

It is an advantage of the invention that a strong CD8+ T cell response is produced.

A 'good' single shot Ad vaccination will give a response in the 100's; a boost is generally
required to get above 1,000 SFU. Thus 'strong' suitably means >800 SFU after a single
30 shot (single administration). Of course the skilled reader will appreciate that this can
be dose dependent - these comments are in the context of the preferred dose given
herein.

For example, it is an advantage of the invention that a strong T cell response is
35 measured even after two weeks following one shot of ChAdOx1- VZV GpE with a mean
response of 1361 (s.e.m. 145 n=5) SFU per 10⁶ splenocytes produced (N.B. ELISpot will
measure CD4+ and CD8+ T cell responses). Previous work with these viral vectors has

demonstrated lower immune responses following one-shot immunisation against variant antigen inserts, for example one shot vaccination with monovalent EBOV in preclinical models induces only 200-500 SFU - showing that the invention produces a much stronger response than the prior art. Moreover, Figure 1 and Figure 2 from prior art Dicks et al 2015 (Vaccine 33 (2015) pages 1121–1128 “The relative magnitude of transgene-specific adaptive immune responses induced by human and chimpanzee adenovirus vectors differs between laboratory animals and a target species”) show much lower immunogenicity, again demonstrating the surprising strength of the responses according to the present invention.

10

It is an advantage of the invention that a sustained T cell response is produced. Unless otherwise apparent from the context, ‘sustained’ means at least 16 weeks.

It is an advantage of the invention that the same vectors can be used to re-vaccinate (i.e. to boost) patients. This may be obtained by priming with ChAdOx1 and boosting with ChAdOx2, or priming with ChAdOx2 and boosting with ChAdOx1. Moreover, the same vector may be used for a boost as used for a prime if the boost is carried out at an interval of at least 6 months from the prime. This may be referred to as “homologous prime-boost”.

20

It is an advantage of the invention that no adjuvant is required. This avoids the disadvantage of the pain/reactogenicity which is experienced when using adjuvants in administration to humans.

It is an advantage of the invention that the compositions are cheaper than adjuvanted vaccines. Adjuvants are complex preparations and can be expensive, such as 20USD per administration. The compositions of the invention require only a single component (i.e. the viral vector containing the antigen as described) and are therefore simpler and cheaper, which is an advantage of the invention.

30

It is an advantage of the invention that live replication deficient viral vectors are used, so the invention is safer than prior art such as Zostavax™.

It is an advantage of the invention that only a single dose is required, so the invention is better than multi-dose prior art such as Shingrix™.

It is an advantage of the invention that only a single composition/ single vial is needed, so the invention is better than adjuvanted prior art such as Shingrix™ which requires

two vials, one of antigen and one of adjuvant, to be transported and stored, and then mixed immediately before injection.

It is an advantage of the invention that immunogenicity is superior to prior art such as Zostavax™ or Shingrix™.

5

Gly E ANTIGEN

By “Gly E antigen” (sometimes referred to as “gE”) is meant the “standard” gE antigen sequence of VZV.

10

In more detail, the original VZV sequence (and strain) used to make the compositions of the invention is suitably the publically disclosed coding sequence as follows:

DEFINITION Human herpesvirus 3 isolate 1140VZV glycoprotein E gene, complete cds

15 ACCESSION (GenBank) AY253715

VERSION AY253715.1:

```

1 atggggacag ttaataaacc tgtggtgggg gtattgatgg ggttcggaat taccacggga
61 acgttgcgta taacgaatcc ggtcagagca tccgtcttgc gatacgatga ttttcacatc
121 gatgaagaca aactggatac aaactccgta tatgagcctt actaccattc agatcatgcg
20 181 gagtcttcat gggtaaatcg gggagagtct tcgcgaaaag cgtacgatca taactcacct
241 tatatatggc cacgtaatga ttatgatgga tttttagaga acgcacacga acaccatggg
301 gtgtataatc agggccgtgg tatcgatagc ggggaacggt taatgcaacc cacacaaatg
361 tctgcacagg aggatcttgg ggacgatacg ggcattccacg ttatccctac gttaaaccggc
421 gatgacagac ataaaattgt aaatgtggac caacgtcaat acggtgacgt gtttaaagga
25 481 gatcttaatc caaaacccca aggccaaaga ctcatgagg tgtcagtgga agaaaatcac
541 ccgtttactt tacgcgcacc gattcagcgg atttatggag tccggtacac cgagacttgg
601 agctttttgc cgtcattaac ctgtacggga gacgcagcgc ccgccatcca gcataatgt
661 ttaaaacata caacatgctt tcaagacgtg gtgggtggatg tggattgcgc ggaaaaact
721 aaagaggatc agttggccga aatcagttac cgttttcaag gtaagaagga agcggaccaa
30 781 ccgtggattg ttgtaaacac gagcacactg tttgatgaac tcgaattaga ccccccgag
841 attgaaccgg gtgtcttgaa agtacttcgg acagaaaaac aatacttggg tgtgtacatt
901 tggaacatgc gcggctccga tggtagctct acctacgcca cgtttttggg caccctggaaa
961 ggggatgaaa aaacaagaaa ccctacgccc gcagtaactc ctcaaccaag aggggctgag
1021 tttcatatgt ggaattacca ctgcgatgta ttttcagttg gtgatacggt tagcttggca
35 1081 atgcatcttc agtataagat acatgaagcg ccatttgatt tgctgttaga gtggttgat
1141 gtcccatcgc atctacatg tcaaccaatg cggttatatt ctacgtgttt gtatcatccc
1201 aacgcacccc aatgcctctc tcatatgaat tccggttgta catttacctc gccacattta
1261 gccagcgtg ttgcaagcac agtgtatcaa aattgtgaac atgcagataa ctacaccgca
1321 tattgtctgg gaatatctca tatggagcct agctttggtc taatcttaca cgacgggggc

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1381 accacgttaa agtttgtaga tacacccgag agtttgtcgg gattatacgt ttttggtg
 1441 tattttaacg ggcatgttga agccgtagca tacactgttg tatccacagt agatcatttt
 1501 gtaaacgcaa ttgaagagcg tggatttccg ccaacggccg gtcagccacc ggcgactact
 1561 aaacccaagg aaattacccc cgtaaaccac ggaacgtcac cacttctacg atatgccgca
 5 1621 tggaccggag ggcttgacgc agtagtactt ttatgtctcg taatattttt aatctgtacg
 1681 gctaaacgaa tgagggttaa agcctatagg gtagacaagt ccccgataa ccaaagcatg
 1741 tattacgctg gccttccagt ggacgatttc gaggactcgg aatctacgga tacggaagaa
 1801 gagtttggtg acgcgattgg agggagtcac ggggggttcga gttacacggt gtatatagat
 1861 aagaccggt ga

- 10 It is the same coding sequence to the following most commonly known VZV strain:
 Human herpesvirus 3 strain Oka vaccine strain.

Suitably the GlyE has the amino acid sequence generated by translating the above-
 referenced coding sequence (cds) using the universal genetic code, i.e. the amino acid
 15 sequence also publically disclosed as

GenBank: AY253715.1:

MGTVNKPVGVLMGFGIITGTLRITNPVRASVLRYYDDFHIDEDKLDTNSVYEPYHSDHAESSW
 VNRGESSRKAYDHNSPYIWPRNDYDGFLNAHEHHGVYNQGRGIDSGERLMQPTQMSAQEDLGD
 DTGIHVIPTLNGDDRHKIVNVDQRQYGDVFKGDLNPKPQGQRLIEVSVEENHPFTLRAPIQRIY
 20 GVRTETWSFLPSLTCTGDAAPAIQHICLKHTTCFQDVVVDVDCAENTKEDQLAEISYRFQGGK
 EADQPWIVVNTSTLFDLELDPPEIEPGVLKVLRTKQYLGVIWNMRGSDGTSTYATFLVTWK
 GDEKTRNPTPAVTPQPRGAEFHMWNYHSHVFSVGDFTSLAMHLQYKIHEAPFDLLEWLYVPID
 PTCQPMRLYSTCLYHPNAPQCLSHMNSGCTFTSPHLAQRVASTVYQNCHEADNYTAYCLGISHM
 EPSFGLILHDGGTTLKFVDTPESLSGLYVFVVYFNGHVEAVAYTVVSTVDHFVNAIEERGFPPT
 25 AGQPPATTKPKEITPVNPGTSPLRLRYAAWTGGLAAVLLCLVIFLICTAKRMRVKAYRVDKSPY
 NQSMYAGLPVDDFEDSESTDTEEEFGNAIGGSHGSSYTVYIDKTR

An exemplary Gly E amino acid sequence is GenBank accession number AAP32865.1 -
 SEQ ID NO: 1. A most suitable GlyE amino acid sequence is SEQ ID NO: 2.

30

Suitably said Gly E antigen comprises SEQ ID NO: 1 or SEQ ID NO: 2.

Suitably said Gly E antigen consists of SEQ ID NO: 1 or SEQ ID NO: 2.

Suitably said Gly E antigen comprises, or consists of, full length Gly E antigen as shown
 35 in SEQ ID NO: 1 or SEQ ID NO: 2.

Suitably said Gly E antigen does not comprise any Truncations /Mutations /Tags
 /Linkers /Fusions compared to the sequence shown in SEQ ID NO: 1 or SEQ ID NO: 2.

bgh Polyadenylation Signal

The bovine growth hormone polyadenylation (bgh-PolyA) signal is a specialised termination sequence for protein expression in eukaryotic cells. This DNA sequence is
5 optionally added to the nucleic acid sequence encoding the GlyE antigen.

An exemplary bgh polyadenylation signal has the sequence shown in SEQ ID NO: 6.

Suitably expression of the antigen is controlled by a standard promoter such as the
10 'long CMV' promoter. An exemplary sequence of the 'long CMV' promoter is shown in SEQ ID NO: 7.

USES

15 Suitably the method is a method of immunising.

In one aspect, the invention relates to a composition comprising an adenoviral vector, said adenoviral vector comprising GlyE.

20 Suitably the composition does not comprise adjuvant. Adjuvant can cause reactogenicity, especially in primates such as humans. Thus it is an advantage that the composition of the invention is effective without adjuvant. Suitably adjuvant is omitted. Suitably the composition consists of elements other than adjuvant. Suitably adjuvant is specifically excluded from the compositions of the invention. Suitably the composition
25 is an adjuvant-free composition.

The invention may be used in prevention of primary VZV infection which causes chickenpox in children and other susceptible individuals.

30 In another aspect, the invention relates to use of a composition as described above in medicine.

In another aspect, the invention relates to use of a composition as described above in the preparation of a medicament for VZV infection. Suitably said medicament is for
35 controlling VZV infection. Suitably said medicament is for preventing resurgence of VZV infection. Suitably said medicament is for controlling shingles. Suitably said medicament is for preventing shingles.

In another aspect, the invention relates to a method for inducing an immune response in a subject, said method comprising administering to said subject a composition as described above.

5

Suitably the immune response comprises cell mediated immunity. Suitably the immune response comprises a T-cell response. Suitably the T-cell response comprises a CD4+ T-cell response.

10 In another aspect, the invention relates to a method comprising administering a first composition comprising an adenovirus based vector and a second composition comprising an adenovirus based vector.

In another aspect, the invention relates to a method comprising administering a first composition comprising a first adenovirus based vector and a second composition
15 comprising a second adenovirus based vector.

Suitably the composition and the second composition are different.

Most suitably the first adenovirus based vector and the second adenovirus based vector are different.

20 Suitably said subject is a mammal.

Suitably said subject is a primate.

Suitably said subject is a human.

The invention also relates to use of a vector, composition or medicament as described
25 herein for treatment of VZV infection.

The invention also relates to use of a vector, composition or medicament as described herein for control of VZV infection.

The invention also relates to use of a vector, composition or medicament as described herein for control of dormant VZV infection.

30 The invention also relates to use of a vector, composition or medicament as described herein for prevention of VZV infection.

The invention also relates to use of a vector, composition or medicament as described herein for prevention of resurgence of VZV infection.

35 COMPOSITIONS

Suitably the composition is an antigenic composition.

Suitably the composition is an immunogenic composition.

Suitably the composition is a vaccine composition.

5

Suitably the composition is a pharmaceutical composition.

Suitably the composition is formulated for administration to mammals, suitably to primates, most suitably to humans.

10

Suitably the composition is formulated taking into account its route of administration. Suitably the composition is formulated to be suitable for the route of administration specified. Suitably the composition is formulated to be suitable for the route of administration selected by the operator or physician.

15

It is an advantage of the invention that the compositions do not require adjuvant. Suitably the compositions of the invention for administration advantageously do not comprise adjuvant. Suitably adjuvant is omitted from compositions of the invention. Most suitably adjuvant is excluded from compositions of the invention. Most suitably the compositions of the invention are adjuvant-free.

20

ADMINISTRATION

In principle any suitable route of administration may be used.

25

Suitably said composition is administered by a route of administration selected from a group consisting of intranasal, oral, aerosol, subcutaneous, intradermal and intramuscular.

More suitably said composition is administered by a route of administration selected from a group consisting of subcutaneous, intradermal and intramuscular.

30

Most suitably said administration is intramuscular.

Suitably the composition of the invention is administered intramuscularly.

Suitably the composition of the invention is formulated for intramuscular administration.

35

Suitably the composition of the invention is given as a single dose.

DOSE

It should be noted that there are alternate ways of describing the dose for adenoviral vectors.

5

Viral particles – vp/mL. This refers to the count of total viral particles administered. Infectious units – i.u./mL. This refers to the number of infectious units administered, and can be correlated more accurately with immunogenicity.

10 By convention, clinical trials in the UK tend to provide the dose in terms of viral particles.

A typical range would be 1×10^7 vp to 1×10^{11} vp, or 1×10^8 vp to 5×10^{11} vp. More suitably a single dose is in the range of 5×10^8 to 5×10^{10} viral particles per administration; more suitably in the range of 5×10^9 to 5×10^{10} viral particles per administration; more suitably in the range of 2.5×10^{10} to 5×10^{10} viral particles per administration, for an adult human.

20 Most suitably the dose is, or is about, 2.5×10^{10} viral particles per administration for an adult human.

Child doses are suitably determined by a physician with reference to the guidance provided herein for adult doses. Exemplary child dose = $\frac{1}{2}$ an adult dose or 1×10^{10} vp/child.

25

Infectious units will depend on the P:I ratio (viral genome:infectivity particle ratio) for any given preparation as is known in the art.

Suitably no adjuvant is administered with the viral vector of the invention.

30

Suitably the viral vector of the invention is formulated with simple buffer. An exemplary buffer may be as shown below under the heading 'Formulation'.

Suitably the composition is administered as a single dose.

35

As used herein, 'adult' means a subject of at least 18 years of age.

As used herein, 'child' means a subject of less than 18 years of age.

Suitably the composition of the invention may be administered to a subject aged 2 years or more, suitably 18 years or more, suitably 60 years or more, suitably 70 years or more, suitably 79 years or more.

Doses are typically determined by a physician taking into account factors such as age, weight, gender or other relevant considerations. Doses given herein are exemplary doses. Unless otherwise indicated, all doses are for 'adult' subjects - child doses may be determined from those e.g. a child dose may be 50% of an adult dose, or more suitably a child dose is as described herein.

10 DATABASE RELEASE

Sequences deposited in databases can change over time. Suitably the current version of sequence database(s) are relied upon. Alternatively, the release in force at the date of filing is relied upon.

As the skilled person knows, the accession numbers may be version/dated accession numbers. The citeable accession numbers for the current database entry are the same as above, but omitting the decimal point and any subsequent digits.

GenBank is the NIH genetic sequence database, an annotated collection of all publicly available DNA sequences (National Center for Biotechnology Information, U.S. National Library of Medicine 8600 Rockville Pike, Bethesda MD, 20894 USA; Nucleic Acids Research, 2013 Jan;41(D1):D36-42) and accession numbers provided relate to this unless otherwise apparent. Suitably the GenBank database release referred to is 15 Dec 2017, NCBI-GenBank Release 223.0.

UniProt (Universal Protein Resource) is a comprehensive catalogue of information on proteins ('UniProt: a hub for protein information' Nucleic Acids Res. 43: D204-D212 (2015)). For the avoidance of doubt, UniProt Release 2015_11 is relied upon.

In more detail, the UniProt consortium European Bioinformatics Institute (EBI), SIB Swiss Institute of Bioinformatics and Protein Information Resource (PIR)'s UniProt Knowledgebase (UniProtKB) Release 2018_01, (31-Jan-2018) is relied upon.

APPLICATIONS

The compositions of the invention may be used as a chicken pox vaccine, most suitably in children. Thus the invention relates to use of the compositions as described above to

prevent chickenpox. In this aspect the composition is administered to infants and/or children and/or adults in at least one dose; suitably said administration is before exposure to generate a protective immune response.

- 5 The compositions of the invention may be used as vaccines in immune-compromised children. In the prior art, children are given the Zostavax™ at a lower dose than adults.

In the art it has occasionally been disclosed that adenovirus may be used as a prime followed by pox virus as a boost. However, according to the present invention it may be
10 observed that applying the vaccine to a person having had previous exposure to VZV means that they may have an existing response (e.g. existing immune response against VZV). By “existing response” suitably is meant the individual has been previously pre-exposed to VZV; this will typically be assessed by measuring seroconversion against VZV surface antigens.

- 15 The U.K. national health service (NHS) describes it as follows: ‘you can have a blood test to check if you have antibodies to the disease, which proves you’ve had chickenpox before.’ <https://www.nhs.uk/conditions/vaccinations/when-is-chickenpox-vaccine-needed/#how-to-check-if-youve-had-chickenpox-before>

Therefore, when a patient has had previous exposure to VZV, administration of the
20 vaccine according to the invention may be regarded as a boost. Thus, in essence the invention may be considered as teaching the use of adenovirus vector as a boost which is a departure from the prior art which teaches that pox viral vectors are best for boosting.

- 25 The VZV from an earlier infection (e.g. having chickenpox as a child) can remain dormant in a patient’s body, such as in the nervous system, and can re-emerge as shingles later in life. A ‘dormant’ VZV infection may be defined as one that is no longer causing an active infection.

- 30 In one embodiment the invention relates to a composition for administration to a mammal comprising an adenoviral vector as described above.

FURTHER APPLICATIONS

- 35 In one aspect, the invention relates to a viral vector comprising nucleic acid having a polynucleotide sequence encoding at least one epitope of the varicella-zoster virus

(VZV) Gly E antigen, wherein said viral vector is an adenoviral vector of human or simian origin.

5 In one aspect, the invention relates to a viral vector comprising nucleic acid having a polynucleotide sequence encoding at least one CD4 T cell and one CD8 T cell epitope of the varicella-zoster virus (VZV) Gly E antigen, wherein said viral vector is an adenoviral vector of human or simian origin.

10 In one aspect, the invention relates to use of a composition as described above in the preparation of a medicament that induces both CD4+ and CD8+ T cell responses to Gly E antigen in a vaccinated subject.

15 In one aspect, the invention relates to use of a composition as described above in the preparation of a medicament that induces both CD4+ and CD8+ T cell responses to Gly E antigen in a vaccinated subject, where that subject is a human.

In one aspect, the invention relates to use of a composition as described above in the preparation of a medicament that induces both CD4+ and CD8+ T cell responses and antibodies to Gly E antigen in a vaccinated subject, where that subject is a human.

20

FURTHER ADVANTAGES

One focus of the invention is the provision of the gE antigen in the context of an adeno vector such as a ChAdOx vector.

25 Here we present data showing the effectiveness of the ChAdOx-gE construct. This has been compared to the existing Zostavax™, and we demonstrate that the construct of the invention is superior.

30 These superior results are better than might be expected based on the known properties of the ChAdOx vector and/or the information on the gE antigen in the art (which combination had never been disclosed in the art).

In particular we show that the inventors' constructs are surprisingly effective, and/or that prejudice in the art would have taught against using this construct, and/or that these constructs are obscure/cryptic/special.

35

Adenoviral vectors are typically used for priming immunisations in the art, whereas pox viral vectors are typically used for boosting applications. It can be observed that since

most people already have some existing T cell response from past infection with Zoster virus (VZV), that we are in fact teaching use of adenoviral vectors for boosting in this invention. This has not been done before for Zoster virus (VZV). Thus in one embodiment the invention relates to a method for boosting pre-existing immune response(s) to VZV in a mammal, by administering a composition as described above to said mammal. In one embodiment the invention relates to a composition as described above for use in boosting pre-existing immune response(s) to VZV in a mammal. Whether or not a mammal possesses pre-existing immune response(s) to VZV may be determined by assessing seroconversion against VZV surface antigens as described above.

A key demonstration of the improvement delivered by the invention is based on the data such as efficacy data shown herein.

In this regard, the inventors are generating excellent T cell responses with the vector of the invention. The existing ZostavaxTM vaccine has focussed on the antibody response. Thus the invention is a measurable improvement over the art. There is the added advantage (which is not expected) that a single dose of an adenovirus as described herein gives as strong a humoral response as a protein and adjuvant. This is a measurable improvement over the art.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a plot

Figure 2 shows a bar chart

Figure 3 shows a graph

Figure 4 shows a plot

Figure 5 shows a sequence alignment. "Insert" means SEQ ID NO: 4 (i.e. an exemplary nucleotide sequence encoding the antigen cassette). "AY253715.1" means SEQ ID NO: 3 (i.e. the wild type nucleotide sequence encoding the GlyE antigen).

Figure 6 shows a sequence alignment (CLUSTAL O(1.2.4) multiple sequence alignment). "vaccine" means SEQ ID NO: 2 (i.e. an exemplary VZV GlyE amino acid sequence antigen cassette). "AY253715.1" means SEQ ID NO: 1 (i.e. the wild type VZV GlyE amino acid sequence).

Figure 7 shows a photograph

Figure 8 shows a plot and a graph

Figure 9 shows four graphs

Figure 10 shows a graph

Figure 11 shows a graph and two plots

Figure 12 shows a bar chart

Figure 13 shows a bar chart

Figure 14 shows a plot

5 **Figure 15** shows a plot

EXAMPLES

Example 1 - Viral Vectored Vaccines Against VZV

10

We have generated viral vectored vaccines toward VZV.

Our data suggest that the vaccine of the invention outperforms a currently licensed prior art Zoster vaccine as assessed for CMI pre-clinically (Figure 1).

15 The higher CMI routinely achieved with viral vectored vaccines, when compared to other vaccine modalities, is likely to translate to higher efficacy, while advantageously only a single shot of viral vectored vaccine may be required for efficacy in contrast to repeated administration of known protein-in-adjuvant vaccines.

We refer to Figure 1.

20 Groups of Balb/c mice (n=5) were vaccinated intramuscularly with 1×10^7 IU of ChAdOx1-VZVgpE or 1×10^7 IU of ChAdOx2-VZVgpE or 1.3×10^3 pfu Zostavax. Splenocytes were collected 2 weeks after final vaccination and the cellular immune response against peptides spanning the whole glycoprotein-E were measured by ELISpot analysis.

25 Responses post ChAdOx1-VZV-gE were significantly higher than those post Zostavax.

This test is in young mice. Age was approx. >8 weeks.

30 It is noted that the prior art Zostavax vaccine can replicate in humans and without wishing to be bound by theory partial immunogenicity may be argued to have come from this. However, it has been demonstrated that non-replicating Zostavax vaccine is comparable in terms of measured immunogenicity to replicating Zostavax in man and can induce a similar immune response.

35 In any case, this is a fair test because none of the vaccines used replicate in mice. Thus it is demonstrated that the invention outperforms prior art Zostavax.

We refer to Figure 2.

8wk⁺ old or aged ex-breeder female Balb/c mice were vaccinated intramuscularly with 1.00E+07iu of ChAdOX1-VZV-gE Mice were culled approx. 2 weeks later and spleen ELISpot performed with peptides spanning the entire VZV gE insert.

- 5 Responses post ChAdOX1-VZV-gE were not significantly different.

This test is in aged mice.

We refer to Figure 3.

- 10 8wk⁺ old female Balb/c mice were vaccinated intramuscularly with ChAdOX1-VZV-gE - **group 1**. 1.00E+07iu ChAdOX1-VZV-gE then four weeks later boosted with 1.00E+07iu ChAdOX1-VZV-gE
ChAdOX2-VZV-gE - **group 2**. 1.00E+07iu ChAdOX2-VZV-gE then four weeks later boosted with 1.00E+07iu ChAdOX2-VZV-gE.
15 Zostavax **group 3**. 1.29E+03 VZV Zostavax then four weeks later boosted with 1.29E+03 VZV Zostavax. Sera was taken at the indicated timepoints and assayed for anti-VZV-gpE specific antibodies.

- The inventors note that Kruskal-Wallis analysis shows with Dunn's multiple
20 comparisons test significant difference in response between group 2 and 3, but not between group 1 and group 3 at 2wk post-boost. This may represent a further advantage of this particular embodiment where the vector is ChAdOx1 i.e. the inventors would not have expected to see antibody response comparable to Zostavax (as evidenced by group 2 - ChAdOx2) but group 1 (ChAdOx1 embodiment) generates a
25 surprisingly good antibody response as well as good T cell responses.
The inventors note that there is no significant difference in responses in figure 4 after one shot antibody responses as 2 weeks or 16 weeks.

- We refer to Figure 4, 8wk⁺ old female Balb/c mice were vaccinated intramuscularly
30 with

lane 1. 1.00E+07iu ChAdOX1-VZV-gE then one week later boosted with 1.00E+07iu ChAdOX1-VZV-gE. (filled box)

lane 1. 1.00E+07iu ChAdOX1-VZV-gE then one week later boosted with 1.00E+07iu ChAdOX2-VZV-gE. (filled circle)

- 35 **lane 2**. 1.00E+07iu ChAdOX1-VZV-gE then four weeks later boosted with 1.00E+07iu ChAdOX1-VZV-gE (filled box)

lane 2. $1.00E+07$ iu ChAdOX1-VZV-gE then four weeks later boosted with $1.00E+07$ iu ChAdOX2-VZV-gE. (filled circle)

lane 3 (no Boost). $1.00E+07$ iu ChAdOX1-VZV-gE (open circle)

5

Mice were culled approx. 2 weeks later and spleen ELISpot performed with peptides spanning the entire VZV gE insert.

10 Thus, lane 3 (no boost) represents a “one-shot” scheme; lanes 2 and 3 ‘filled boxes’ represent ‘homologous prime-boost’ schemes; lanes 2 and 3 ‘filled circle’ represent ‘heterologous prime-boost’ schemes. It could be argued that a heterologous second shot does not show augmentation - however, augmentation might be expected to show at a later time point - this is considered to be due to a response-curve effect.

15 Responses post ChAdOx1-VZV-gE were not significantly different across in young or aged animals for single-administration applications.

A preferred interval between prime and boost (in prime-boost applications; overall single-administration embodiments are preferred) is 4 weeks; when prime and boost
20 are both Ad vectors, the interval may be for example 2, 4, 6 or 8 weeks.

Mouse Model System

25 Regarding the mouse model system for testing these vaccines, it should be noted that a non-replicating zoster virus can give the same response as a replicating zoster virus in humans. Therefore, the mouse data presented herein do indeed represent a fair comparison since although the prior art Zostavax™ does induce a limited infection in humans which is important to boosting the immune response, neither the adenoviral vector constructs of the invention nor the Zostavax prior art comparator can replicate
30 in mice, and therefore the data provided in the application comparing those to formulations in mice are indeed fair and indicative of the superior properties of the vectors according to the invention.

Example 2: Vectors of the invention express efficiently

35

We present western blot analysis of viral vector expression of VZVgE. Subconfluent HEK293T (ChAdOx 1) were infected with viruses with at the indicated MOI. Cells were

harvested 18h later, lysed and protein supernatant lysate run on a Biorad 4-12% gradient gel and probed with a 1:1000 dilution of abcam 52549 VZV in 0.05% PBST and expression detected with ECL reagent.

Results are shown in Figure 7; lanes are as follows:

- 5 0 - molecular markers
- 1 - ChAdOx1 VZVgpE MOI 1 on HEK293T
- 2 - ChAdOx1 VZVgpE MOI 5 on HEK293T
- 3 - ChAdOx2 VZVgpE MOI 1 on HEK293T
- 4 - ChAdOx2 VZVgpE MOI 5 on HEK293T
- 10 5 - VZV +ve control ~100ng
- 6 - VZV +ve control ~500ng

Thus it is demonstrated that the compositions of the invention produce expression of the antigen in human cells.

15 **Example 3: Immunogenicity Of Viral Vectors Encoding Varicella Zoster Virus Glycoprotein E**

We demonstrate cellular immunogenicity after one-shot vaccination against VZV.

- 20 We refer to Figure 8A. Groups of Balb/c mice (n=5) were vaccinated intramuscularly with 1×10^7 IU of ChAdOx1-VZVgpE or 1×10^7 IU of ChAdOx2-VZVgpE or 1.3×10^3 pfu Zostax. Splenocytes were collected 2 weeks after final vaccination and the cellular immune response against peptides spanning the whole glycoprotein-E were measured by ELISpot analysis.

- 25 We refer to Figure 8B. Groups of Balb/c mice (n=5, typically aged 8-10 weeks unless otherwise indicated) were vaccinated intramuscularly with 1×10^7 IU of ChAdOx1-VZVgpE ('aged mice' are ex-breeders and typically >24wk of age) or 1.3×10^3 pfu Zostax. Splenocytes were collected at the times indicated after final vaccination and the cellular immune response against peptides spanning the whole glycoprotein-E were measured
- 30 by ELISpot analysis.

- These ELISpot data show that a cellular immune response, as demonstrated by the T cell response, is induced according to the invention. The response is evident at 2 weeks. The response is induced by a single administration. The response is induced by
- 35 a single dose. The response is a sustained response as shown by the data at the 16week timepoints.

We refer to Figure 9. The cellular immune response of the same groups of Balb/c mice as in Fig 8 were assessed by Intracellular Cytokine Staining (ICS). As before (n=5, typically aged 8-10 weeks unless otherwise indicated) were vaccinated intramuscularly with 1×10^7 IU of ChAdOx1-VZVgpE ('aged mice' are ex-breeders and typically >24wk of age) or 1.3×10^3 pfu Zostax. Spleenocytes were collected at the times indicated after final vaccination and the cellular immune response toward epitopes spanning the whole glycoprotein-E were measured by ICS analysis.

Fig 9A shows the percentage of CD8+T cells secreting IFN- γ after stimulation with VZVgpE peptides and adjusted for background levels of secretion.

Fig 9B shows the percentage of CD4+T cells secreting IFN- γ after stimulation with VZVgpE peptides and adjusted for background levels of secretion.

Fig 9C shows the percentage of IFN- γ + CD8+T cells secreting TNF α and/or IL2 after stimulation with VZVgpE peptides and adjusted for background levels of secretion.

Fig 9D shows the percentage of IFN- γ + CD4+T cells secreting TNF α and/or IL2 after stimulation with VZVgpE peptides and adjusted for background levels of secretion.

Thus overall these FACS sorted experiments show that triple secreting CD4+ T cells (which are very good as without wishing to be bound by theory they are considered the most protective) are induced according to the invention. The data also show induction of CD8+ T cells, which are also very beneficial.

We refer to Figure 10 which shows humoral immunity after one-shot vaccination against VZV. Groups of Balb/c mice (n=5, aged 8-10 weeks unless otherwise indicated) were vaccinated intramuscularly with 1×10^7 IU of ChAdOx1-VZVgpE ('aged mice' are ex-breeders and typically >24wk of age) or 1.3×10^3 pfu Zostax. Sera were collected at the times indicated after final vaccination and the humoral immune response toward affinity purified glycoproteins of Varizella Zoster Virus (Strain Ellen) were measured by ELISA.

For clarity please note that Figures 8B, 9 and 10 show data from the same experiments.

It is a surprising benefit that the immunisations according to the present invention are also effective in raising/inducing antibody titers, despite the one-shot administration. It is a surprising benefit that the invention is as good as prior art compositions such as Zostavax for the induction of antibody responses.

Example 4: Prime-Boost Study

We demonstrate immunogenicity after prime-boost vaccination against VZV.

We refer to Figure 11A.

- 5 8wk⁺ old female Balb/c mice were vaccinated intramuscularly with
ChAdOX1-VZV-gE - group 1. 1.00E+07iu ChAdOX1-VZV-gE then four weeks later
boosted with 1.00E+07iu ChAdOX1-VZV-gE
ChAdOX2-VZV-gE - group 2. 1.00E+07iu ChAdOX2-VZV-gE then four weeks later
boosted with 1.00E+07iu ChAdOX2-VZV-gE.
10 Zostavax - group 3. 1.29E+03 VZV Zostavax then four weeks later boosted with
1.29E+03 VZV Zostavax. Sera was taken at the indicated timepoints and assayed for
anti-VZV-gpE specific antibodies.

- Referring to Figure 11B & Figure 11C, groups of Balb/c mice (n=5, aged 8-10 weeks
15 unless otherwise indicated) were vaccinated intramuscularly with 1 x 10⁷IU of
ChAdOx1-VZVgpE and either not boosted (no boost) or boosted after 1 OR 4 weeks with
1 x 10⁷IU of ChAdOx1-VZVgpE (homologous boost) or 1 x 10⁷IU of ChAdOx2-VZVgpE
(heterologous boost) **a.** Splenocytes were collected 2 weeks after final vaccination and
the cellular immune response against peptides spanning the whole glycoprotein-E were
20 measured by ELISpot analysis. **b.** Sera were collected 2 weeks after final vaccination
and the humoral immune response toward affinity purified glycoproteins of Varizella
Zoster Virus (Strain Ellen) were measured by ELISA.

- These data show that the single-shot or single-administration embodiments of the
25 invention provide as good a response as a prime-boost regime. Thus it is an advantage
of the invention that only a single shot or single dose (single administration) is needed.

Example 5: Comparative Study

- 30 The inventors compare the composition of the invention to prior art Shingrix™ across 3
doses and after one shot.

- Humoral immunity after one-shot vaccination against VZV was tested. Groups of CD1
mice (n=7/8) were vaccinated intramuscularly with either ChAdOx1-VZVgpE or
35 Shingrix™, at doses indicated (3 doses). Sera were collected at 4 weeks indicated after
vaccination and the humoral immune response toward affinity purified glycoproteins of

Varizella Zoster Virus (Strain Ellen) were measured by ELISA. We refer to Figure 12. Mean with s.e.m. depicted.

Vaccine Description	Group
Shingrix™ low dose 0.2µg/mouse	1
Shingrix™ mid dose 1µg/mouse	2
Shingrix™ high dose 5µg/mouse	3
ChAdOx1-VZVgpE low 1×10^6 /mouse	4
ChAdOx1-VZVgpE mid 1×10^7 /mouse	5
ChAdOx1-VZVgpE high 1×10^8 /mouse	6

- 5 Cellular immunogenicity after one-shot vaccination against VZV was tested. Groups of CD1 mice (n=7/8) were vaccinated intramuscularly with either ChAdOx1-VZVgpE or Shingrix™, at doses indicated (3 doses). Splenocytes were collected 4 weeks after final vaccination and the cellular immune response against peptides spanning the whole glycoprotein-E were measured by ELISpot analysis. We refer to Figure 13. Mean with
- 10 s.e.m. depicted.

Vaccine Description	Group
Shingrix™ low dose 0.2µg/mouse	1
Shingrix™ mid dose 1µg/mouse	2
Shingrix™ high dose 5µg/mouse	3
ChAdOx1-VZVgpE low 1×10^6 /mouse	4
ChAdOx1-VZVgpE mid 1×10^7 /mouse	5
ChAdOx1-VZVgpE high	6

1*10 ⁸ /mouse	
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Example 6: Comparative Study

- Groups of outbred CD-1 mice (n=8) were vaccinated intramuscularly with
- 5 **Group 1;** 1ug of Shringrix with ASO1B adjuvant and four weeks later the animals were boosted with 1ug of Shringrix with ASO1B adjuvant or
- Group 2;** no prime and four weeks later the animals were vaccinated with 1.3 x 10³pfu Zostavax or
- 10 **Group 3;** 1.3 x 10³pfu Zostavax and four weeks later animals were boosted with 1 x 10⁷IU of ChAdOx1-VZVgpE or
- Group 4;** no prime and four weeks later the animals were vaccinated 1 x 10⁷IU of ChAdOx1-VZVgpE or
- Group 5;** naïve animals.
- 15 We refer to Figure 14. The mean and standard error of the mean are depicted. Serum was collected approximately three weeks after final vaccination and analysed for anti- VZVgpE antibodies.

- Kruskal-Wallis analysis with Dunn's multiple comparison test demonstrates that
- 20 **Group 1;** two shots of protein with adjuvant induces a significantly higher antibody titre when compared to **Group 2;** one shot of Zostavax or **Group 4;** one shot of ChAdOx1-VZVgpE, this result is as expected. However, there was no difference in the level of antibodies measured between **Group 1** and **Group 3**. This is not expected, as ChAdOx1 after Zostavax would not be predicted to increase the humoral immune
- 25 response to a comparable level of two shots of adjuvanted protein. This is an advantage, as currently UK adults aged 70 or over have been recommended to receive Zostavax vaccination, here we demonstrate that a boost vaccination of ChAdOx1-VZV-gpE can augment the antibody titres to those levels measured after two protein and adjuvant vaccinations, a regimen that is associated with efficacy of 91% or higher.

30

Dunn's multiple comparisons test	Significant?	Summary	Adjusted P Value
Shingrix 1ug/mouse x2 vs. Zostavax-ChAdOx1-gE	No	ns	>0.9999
Shingrix 1ug/mouse x2 vs. ChAdOx1-gE x1	Yes	*	0.0172
Shingrix 1ug/mouse x2 vs. Zostavax x1	Yes	**	0.0019

Example 7: Comparative Study

- Groups of C57BL6 mice (n=5) were vaccinated intramuscularly with
- 5 **Group 1;** 1ug of Shringrix with ASO1B adjuvant and four weeks later the animals were boosted with 1ug of Shringrix with ASO1B adjuvant or
- Group 2;** no prime and four weeks later the animals were vaccinated with 1.3×10^3 pfu Zostavax or
- Group 3;** 1.3×10^3 pfu Zostavax and four weeks later animals were boosted with 1×10^7 IU of ChAdOx1-VZVgpE or
- 10 **Group 4;** no prime and four weeks later the animals were vaccinated 1×10^7 IU of ChAdOx1-VZVgpE.

- We refer to Figure 15. The mean and standard error of the mean are depicted.
- 15 Splenocytes were collected approximately four weeks after final vaccination and analysed for NK maturity and secretion of cytokines. Kruskal-Wallis analysis with Dunn's multiple comparison test demonstrates that NK cells after a prime-boost vaccination of 1.3×10^3 pfu Zostax followed by 1×10^7 IU of ChAdOx1-VZVgpE secrete
- 20 more IFN-g (**Group 3**) when compared to the Shringrix vaccination (**Group 1**). This is not expected and offers an advantage, NK cell activation has previously been demonstrated to augment the adaptive immune response and this strong induction of the innate immune response by ChAdOx1-VZVgpE after a Zostavax prime is not expected. Additionally, NK cells have been demonstrated to be critically important in
- 25 mediating immunity against VZV infection (PMID; 2543925, 30565241).

Table of sequences

SEQ ID NO: 1	wild type VZV GlyE amino acid sequence
SEQ ID NO: 2	exemplary VZV GlyE amino acid sequence
SEQ ID NO: 3	wild type nucleotide sequence encoding VZV GlyE (Genbank accession number AY253715.1; this is the nucleotide sequence encoding the amino acid sequence of accession number AAP32865.1 - SEQ ID NO: 1: (AAP32865.1 glycoprotein E [Human alphaherpesvirus 3]))
SEQ ID NO: 4	exemplary nucleotide sequence encoding VZV GlyE codon-optimised for humans
SEQ ID NO: 5	ChAdOx2: Viral vector based on Chimpanzee adenovirus C68
SEQ ID NO: 6	bgh polyadenylation signal
SEQ ID NO: 7	exemplary sequence of long CMV promoter

Please note that 'Gly E' means glycoprotein E, and is sometimes referred to as 'gE'.

- 5 In one embodiment Gly E sequence having similarity to antigen insert SEQ ID NO: 1 of 50% or less may be used. In one embodiment Gly E sequence having similarity to antigen insert SEQ ID NO: 1 of 50% or more may be used, suitably 60% or more, suitably 70% or more, suitably 80% or more, suitably 90% or more, suitably 95% or more.

10

SEQUENCE LISTING

SEQ ID NO: 1: exemplary Gly E sequence - GenBank accession number AAP32865.1 - (>AAP32865.1 glycoprotein E [Human alphaherpesvirus 3])(also

- 15 known as the amino acid sequence encoded by GenBank nucleotide accession number AY253715.1):

```
MGTVNKPVVGVLMGFGIITGLRITNPVRASVLRYYDDFHIDEDKLDNTNSVYEPYYHSDHAESSWVNRGESSRKAYDHN
SPYIWP RNDYDGFLENAHEHHGVYNQGRGIDSGERLMQPTQMSAQEDLGDDTGIHVITPLNGDDRHKIVNVDQRQYGD
VFKGDLNPKPQGQRLIEVSVEENHPFTLRAPIQRIYGVRYTETWSFLPSLTCTGDAAPAIQHICLKHTTCFQDVVVDV
```

5 DCAENTKEDQLAEISYRFQGGKEADQPWIVVNTSTLFDELELDPPEIEPGVLKVLRTKQYLGVIWNMRGSDGTSTY
ATFLVTWKGDDEKTRNPTPAVTPQPRGAEFHWMNYHSHVFSVGDTFSLAMHLQYKIHEAPFDLLEWLYVPIDPTCQPM
RLYSTCLYHPNAPQCLSHMNSGCTFTSPHLAQRVASTVYQNCHEADNYTAYCLGISHMEPSFGLILHDGGTTLKFDVT
PESLSGLYVFVVFYFNHVEAVAYTVVSTVDHFVNAIEERGFPTAGQPPATTKPKEITPVNPGTSPLLRYAAWTGGLA
AVVLLCLVIFLICTAKRMRVKAYRVDKSPYNQSMYYAGLPVDDFEDSESTDTEEEFGNAIGGSHGGSSYTVYIDKTR

SEQ ID NO: 2 exemplary VZV GlyE cassette amino acid sequence (sometimes referred to as "Insert- protein") :

10 MGTVNKPVVGLMGFGIITGTLRITNPVRASVLRYYDFHIDEDKLDTNVSYEPYHSDHA
ESSWVNRGESSRKAYDHNSPYIWPRNDYDGFLENAHEHHGVYNQGRGIDSGERLMQPTQM
SAQEDLGGDDTGIHVIPITLNGDDRHKIVNVDQRQYGDVFKGDLNPKPQGRLIEVSVEENH
PFTLRAPIQRIYGVRYTETWSFLPSLTCTGDAAAPAIQHICLKHTTCFQDVVDVDCAENT
KEDQLAEISYRFQGGKEADQPWIVVNTSTLFDELELDPPEIEPGVLKVLRTKQYLGVI
15 WNMRGSDGTSTYATFLVTWKGDDEKTRNPTPAVTPQPRGAEFHWMNYHSHVFSVGDTFSLA
MHLQYKIHEAPFDLLEWLYVPIDPTCQPMRLYSTCLYHPNAPQCLSHMNSGCTFTSPHL
AQRVASTVYQNCHEADNYTAYCLGISHMEPSFGLILHDGGTTLKFDVTPESLSGLYVFV
YFNHVEAVAYTVVSTVDHFVNAIEERGFPTAGQPPATTKPKEITPVNPGTSPLLRYAA
WTGGLA
20 AVVLLCLVIFLICTAKRMRVKAYRVDKSPYNQSMYYAGLPVDDFEDSESTDTEE
EFGNAIGGSHGGSSYTVYIDKTR

SEQ ID NO: 3 - wild type nucleotide sequence encoding VZV GlyE (Genbank accession number AY253715.1; this is the nucleotide sequence encoding the amino acid sequence of accession number AAP32865.1 - SEQ ID NO: 1: (AAP32865.1 glycoprotein E

25 [Human alphaherpesvirus 3]))):
ATGGGGACAGTTAATAAACCTGTGGTGGGGTATTGATGGGGTTCGGAATTATCACGGGAACGTTGCGTATAACGAAT
CCGGTCAGAGCATCCGTCTTGCGATACGATGATTTTCACATCGATGAAGACAACTGGATACAACTCCGTATATGAG
CCTTACTACCATTAGATCATGCGGAGTCTTCATGGGTAAATCGGGGAGAGTCTTCGCGAAAAGCGTACGATCATAAC
TCACCTTATATATGCCCACGTAATGATTATGATGGATTTTATAGAGAACGCACACGAACACCATGGGGTGTATAATCAG
30 GGCCGTGGTATCGATAGCGGGGAACGGTAAATGCAACCCACACAAATGTCTGCACAGGAGGATCTTGGGGACGATACG
GGCATCCACGTTATCCCTACGTTAAACGGCGATGACAGACATAAAATTGTAAATGTGGACCAACGTCAATACGGTGAC
GTGTTTAAAGGAGATCTTAATCCAAAACCCCAAGGCCAAAGACTCATTGAGGTGTCAGTGAAGAAAATCACCCGTTT
ACTTTACGCGCACCGATTACGCGGATTTATGGAGTCCGGTACACCGAGACTTGGAGCTTTTGGCCGTATTAACTGT
ACGGGAGACGCAGCGCCGCCATCCAGCATATATGTTTAAACATACAACATGCTTTCAAGACGTGGTGGTGGATGTG
35 GATTGCGCGGAAAATACTAAAGAGGATCAGTTGGCCGAAATCAGTTACCGTTTCAAGGTAAGAAGGAAGCGGACCAA
CCGTGGATTGTTGTAAACACGAGCACACTGTTTGATGAATCGAATTAGACCCCCCGAGATTGAACCGGGTGTCTTG
AAAGTACTTCGACAGAAAAACAATACTTGGGTGTGTACATTGGAACATGCGCGGCTCCGATGGTACGTCTACCTAC
GCCACGTTTTTGGTCACCTGGAAAGGGGATGAAAAACAAGAAACCTACGCCCGCAGTAACTCCTCAACCAAGAGGG
GCTGAGTTTCATATGTGAATTACCACTCGCATGTATTTTCAGTTGGTGATACGTTTAGCTTGGCAATGCATCTTCAG
40 TATAAGATACATGAAGCGCCATTTGATTTGCTGTTAGAGTGGTTGTATGTCCCCATCGATCCTACATGTCAACCAATG
CGGTTATATTCTACGTGTTTGTATCATCCCAACGCACCCCAATGCCTCTCTCATATGAATCCGGTTGTACATTTACC
TCGCCACATTTAGCCAGCGTGTGCAAGCACAGTGTATCAAAATTGTGAACATGCAGATAACTACACCGCATATTGT
CTGGGAATATCTCATATGGAGCCTAGCTTTGGTCTAATCTTACACGACGGGGCACCACGTTAAAGTTTGTAGATACA
CCCGAGAGTTTGTGGGATTATACGTTTTTGGTGTATTTTAAACGGGCATGTTGAAGCCGTAGCATACACTGTTGTA
45 TCCACAGTAGATCATTTGTAAACGCAATTGAAGAGCGTGGATTTCCGCCAACGGCCGGTCAGCCACCGCGGACTACT

AAACCCAAGGAAATTACCCCCGTAAACCCCGGAACGTCACCACTTCTACGATATGCCGCATGGACCGGAGGGCTTGCA
GCAGTAGTACTTTTATGTCTCGTAATATTTTAACTCTGTACGGCTAAACGAATGAGGGTTAAAGCCTATAGGGTAGAC
AAGTCCCCGTATAACCAAAGCATGTATTACGCTGGCCTTCCAGTGGACGATTTCGAGGACTCGGAATCTACGGATACG
GAAGAAGAGTTTGGTAACGCGATTGGAGGGAGTCACGGGGGTTTCGAGTTACACGGTGTATATAGATAAGACCCGGTGA

5

SEQ ID NO: 4 - exemplary nucleotide sequence encoding VZV GlyE antigen
cassette/expression cassette (sometimes referred to as ">Insert- Vaccine")

ATGGGCACCGTGAACAAGCCCGTCTGTTGGCGTGCTGATGGGCTTCGGCATCATCACCGGCACCTGCGGATACCAAT
10 CCTGTGCGGGCCAGCGTGCTGAGATACGACGACTTCCACATCGACGAGGACAAGCTGGACACCAACAGCGTGACGAG
CCCTACTACCACAGCGACCACGCCGAGAGCAGCTGGGTCAACAGAGGCGAGTCCAGCCGGAAGGCCATACGACCACAA
AGCCCCATACATCTGGCCCCGGAACGACTACGACGGCTTCCTGGAAAATGCCACGAGCACCACGGCGTGTAACACG
GGCAGAGGCATCGACAGCGGCGAGAGACTGATGCAGCCACCCAGATGAGCGCCAGGAAGATCTGGGCGACGACACC
GGCATCCACGTGATCCCTACCTGAACGGCGACGACGGGCACAAGATCGTGAACGTGGACCAGCGGCAGTACGGCGAC
15 GTGTTCAAGGGCGACCTGAACCCCAAGCCCCAGGGACAGCGGCTGATTGAGGTGTCCGTGGAAGAGAACCACCCCTTC
ACCCTGAGAGCCCCATCCAGAGAATCTACGGCGTGCGCTATACCGAGACTTGGAGCTTCCTGCCAGCCTGACCTGT
ACTGGCGACGCCGCTCCTGCCATCCAGCACATCTGCCTGAAGCACACCACCTGTTTCAGGACGTGGTGGTGGACGTG
GACTGCGCCGAGAACACCAAGAGGACCAGCTGGCCGAGATCAGTACCGGTTCCAGGGCAAGAAAGAGGCCGACCAG
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20 AAGGTGCTGCGGACCGAGAAGCAGTACCTGGGAGTGTACATCTGGAACATGCGGGGACGACGCGCACCTCTACCTAC
GCCACCTTCCTCGTGACCTGGAAGGGCGACGAGAAAACCCGGAACCTACCCCTGCCGTGACCCCTCAGCCTAGAGGC
GCCGAGTTTACATGTGAATTACCACAGCCACGTGTTACGCGTGGGCGACACCTTCTCCCTGGCCATGCATCTGCAG
TACAAGATCCACGAGGCCCCCTTCGACCTGCTGCTGGAATGGCTGTACGTGCCATCGACCTACCTGCCAGCCCATG
CGGCTGTACTCCACCTGTCTGTACCACCCCAACGCCCCCAGTGCCTGAGCCACATGAATAGCGGCTGCACCTTCACC
25 AGCCCCACCTGGCTCAGAGGGTGGCCAGCACCGTGTACCAGAATTGCGAGCACGCCGACAATAACACCGCCTACTGC
CTGGGCATCAGCCACATGGAACCTAGCTTCGGCCTGATCCTGCACGACGGCGGCACACCTGAAGTTCGTGGATACC
CCAGAGAGCCTGAGCGGCTGTACGTGTTCTGTGGTGTACTTCAACGGCCACGTGGAAGCCGTGGCTACACCGTGGTG
TCCACCTGAGACCTTCGTGAACGCCATCGAGGAACGGGGCTTCCTCCAACTGCTGGACAGCCTCCTGCCACCACC
AAGCCCAAAGAAATCACCCCGTGAACCCCGGCACCAGCCCTCTGCTGCGCTATGCTGCTTGGACAGGCGGACTGGCT
30 GCTGTGGTGTGCTGTGCTCGTCTGATTTTCTGATCTGCACCGCCAAGCGGATGAGAGTGAAGGCCTATCGGGTGGAC
AAGTCCCCCTACAACAGAGCATGTACTACGCCGGCTGCCCGTGGACGATTTCGAGGATAGCGAGACCGGACACC
GAGGAAGAGTTTCGGCAACGCCATTGGCGGGCTCTACGGCGGCAGCAGCTATACCGTGTACATCGACAAGACCCGCTGA

SEQ ID NO: 5

35 ChAdOx2: Viral vector based on Chimpanzee adenovirus C68
ccatcttcaa taatatacct caaacttttt gtgcgcgtta atatgcaaat gaggcgtttg 60
aatattggga ggaagggcgg tgattggtcg agggatgagc gaccgttagg ggcggggcga 120
gtgacgtttt gatgacgtgg ttgcgaggag gagccagttt gcaagtcttc gtgggaaaag 180
tgacgtcaaa cgaggtgtgg tttgaacacg gaaatactca attttccgc gctctctgac 240
40 aggaaatgag gtgtttctgg gcggtgcaa gtgaaaacgg gccattttcg cgcgaaaact 300
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gggcccagta gactttgacc gattacgtgg gggtttcgat taccgtgttt ttcacctaaa 420
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agtttgtaca aaaaagctga acgagaaacg taaaatgata taaatatcaa tatattaaat 540

tagatttttgc ataaaaaaca gactacataa tactgtaaaa cacaacatat ccagtccacta 600
 tggcgggcgc cgattttattc aacaaagcca cgttgtgtct caaaatctct gatgtttacat 660
 tgcacaagat aaaaatatat catcatgaac aataaaactg tctgcttaca taaacagtaa 720
 tacaaggggt gttatgagcc atattcaacg ggaacgtct tgcctgaggc cgcgattaaa 780
 5 ttccaacatg gatgctgatt tatatgggta taaatgggct cgtgataatg tcgggcaatc 840
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 tggcaaaggt agcgttgcca atgatgttac agatgagatg gtcagactaa actggctgac 960
 ggaatttatg cctcttccga ccatcaagca ttttatccgt actcctgatg atgcatgggt 1020
 actcaccact gcgattcccc ggaaaacagc attccaggta ttagaagaat atcctgatcc 1080
 10 aggtgaaaaa attgttgatg cgctggcagt gttcctgcgc cggttgcatt cgattcctgt 1140
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 gaataacggt ttggttgatg cgagtgtatt tgatgacgag cgtaatggct ggctgttga 1260
 acaagtctgg aaagaaatgc ataagcttt gccattctca ccgattcag tcgtcactca 1320
 tgggtgatttc tcaattgata accttatttt tgacgagggg aaattaatag gttgtattga 1380
 15 tgttggaaca gtcggaatcg cagaccgata ccaggatctt gccatcctat ggaactgcct 1440
 cggtagtatt tctccttcat tacagaaacg gctttttcaa aaatatggta ttgataatcc 1500
 tgatataaat aaattgcagt ttcatttgat gctcgatgag tttttctaata cagaattggt 1560
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 cgtatttgcg cgctgatttt tgccgtataa gaatatatac tgatatgtat acccgaagta 1680
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 gaggtcgcgc ggtttattga aatgaacgac tcttttgctg acgagaacag gggctggtga 1920
 aatgcagttt aaggtttaca cctataaaag agagagccgt tatcgtctgt ttgtggatgt 1980
 25 acagagtgat attattgaca cgcgcggcg acggatggtg atccccctgg ccagtgcacg 2040
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 aatataaatg tcaggctccc ttatacacag ccagtctgca ggtcgacct agtgactgga 2280
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 tccagcaaac cctccacgag cacatccaga aacaagagga cagcgaaagc gggagcgttt 29460
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 25 tcgcgagagc cgcctccac cggcattctt aagcacacc tcataattcc aagagattct 29640
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 cccagtgwgc attgccaaat gtaagattga aataagcatg ctggctagac cctgtgatat 29880
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 acggggtctc cggcgcgacc ctctagaag ctgtcgccat gattgaaaag catcaccgag 30180
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 45 ttcaaacacc tcatttgcatt attaacgcgc aaaaaagtt tgaggatatat tattgatgat 30840
 gg 30842

SEQ ID NO: 6 - bgh polyadenylation signal

ctgtgecttctagttgccagccatctgttgtttgcccctcccccgctgecttcccttgaccctggaaggtgccactccca
 ctgtccttttcctaataaaatgaggaaattgcatcgcatgtctgagtaggtgtcattctattctggggggtgggtgg
 5 ggcaggacagcaagggggaggattgggaagacaatagcaggcatgctggggatgcggtgggctctatgg

SEQ ID NO: 7: long CMV promoter

ATCGCCATTTTTCCAAAAGTGATTTTTGGGCATACGCGATATCTGGCGATAGCGCTTA
 TATCGTTTACGGGGGATGGCGATAGACGACTTTGGTGACTTGGGCGATTCTGTGTGT
 10 CGCAAATATCGCAGTTTCGATATAGGTGACAGACGATATGAGGCTATATCGCCGATA
 GAGGCGACATCAAGCTGGCACATGGCCAATGCATATCGATCTATACATTGAATCAATA
 TTGGCCATTAGCCATATTATTTCATTGGTTATATAGCATAAATCAATATTGGCTATTGG
 CCATTGCATACGTTGTATCCATATCATAATATGTACATTTATATTGGCTCATGTCCAAC
 ATTACCGCCATGTTGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGGG
 15 TCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCC
 CGCCTGGCTGACCGCCCAACGACCCCCGCCCATTTGACGTCAATAATGACGTATGTTCC
 CATAGTAACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAA
 ACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACG
 TCAATGACGGTAAATGGCCCGCTGGCATTATGCCCAGTACATGACCTTATGGGACTT
 20 TCCTACTTGGCAGTACATCTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTT
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 CACCCCATTTGACGTCAATGGGAGTTTGT TTTGGCACCAAAATCAACGGGACTTTCCAA
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 AGGTCTATATAAGCAGAGCTCTCCCTATCAGTGATAGAGATCTCCCTATCAGTGATAG
 25 AGATCGTCGACGAGCTCGTTTGTGTAACCGTCAGATCGCCTGGAGACGCCATCCACG
 CTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGCGGCCGGGAACG
 GTGCATTGGAACGCGGATTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGT
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 ATACACCCCCGCTTCCTCATGTTATAGGTGATGGTATAGCTTAGCCTATAGGTGTGGG
 30 TTATTGACCATTATTGACCACTCCCTATTGGTGACGATACTTTCCATTACTAATCCAT
 AACATGGCTCTTTGCCACAACCTCTCTTTATTGGCTATATGCCAATACACTGTCTTCAG
 AGACTGACACGGACTCTGTATTTTTACAGGATGGGGTCTCATTTATTATTTACAAATT
 CACATATACAACACCACCGTCCCCAGTGCCCGCAGTTTTTTATTAAACATAACGTGGGA
 TCTCCACGCGAATCTCGGGTACGTGTTCCGGACATGGGCTCTTCTCCGGTAGCGGCG
 35 GAGCTTCTACATCCGAGCCCTGCTCCCATGCCTCCAGCGACTCATGGTCTGCTCGGCAG
 CTCCTTGCTCCTAACAGTGGAGGCCAGACTTAGGCACAGCACGATGCCACCACCACC
 AGTGTGCCGCACAAGGCCGTGGCGGTAGGGTATGTGTCTGAAAATGAGCTCGGGGA
 GCGGGCTTGCACCGCTGACGCATTTGGAAGACTTAAGGCAGCGGCAGAAGAAGATGC

AGGCAGCTGAGTTGTTGTGTTCTGATAAGAGTCAGAGGTAAC TCCCGTTGCGGTGCT
GTTAACGGTGGAGGGCAGTGTAGTCTGAGCAGTACTCGTTGCTGCCGCGCGGCCAC
CAGACATAATAGCTGACAGACTAACAGACTGTTCCCTTCCATGGGTCTTTCTGCA

CLAIMS

1. A composition comprising a viral vector comprising nucleic acid having a polynucleotide sequence encoding at least one epitope of the varicella-zoster virus (VZV) Gly E antigen, wherein said viral vector is an adenoviral vector.
2. A composition according to claim 1 wherein said at least one epitope comprises at least one CD4 T cell epitope and at least one CD8 T cell epitope.
3. A composition according to claim 1 or claim 2 wherein said adenoviral vector is of human or simian origin.
4. A composition according to any of claims 1 to 3 wherein said adenoviral vector is ChAdOx 1 or ChAdOx 2.
5. A composition according to any preceding claim wherein said composition is adjuvant-free.
6. A composition according to any preceding claim wherein said Gly E antigen has the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2, suitably SEQ ID NO: 2.
7. A composition according to any preceding claim wherein said polynucleotide sequence comprises the sequence of SEQ ID NO: 3 or SEQ ID NO: 4, suitably SEQ ID NO: 4.
8. A composition according to any preceding claim wherein said polynucleotide sequence further comprises the sequence of the bgh polyadenylation signal SEQ ID NO: 6.
9. A composition according to any preceding claim wherein said polynucleotide sequence encoding at least one epitope of the varicella-zoster virus (VZV) Gly E antigen is operably connected to the long CMV promoter, suitably the long CMV promoter has the nucleotide sequence of SEQ ID NO: 7.
10. A composition according to any of claims 1 to 9 wherein said viral vector sequence is as in ECACC accession number 12052403 (ChAdOx1).

11. A composition according to any of claims 1 to 9 wherein said viral vector sequence is as in SEQ ID NO: 5 (ChAdOx2).
12. A composition according to any preceding claim wherein administration of a single dose of said composition to a mammalian subject induces protective immunity in said subject.
13. A composition according to any preceding claim for induction of an immune response against VZV.
14. A composition according to any preceding claim for induction of an immune response against VZV, wherein a single dose of said composition is administered.
15. A composition according to any of claims 1 to 14 for induction of an immune response against VZV, wherein said composition is administered once.
16. A composition according to any of claims 1 to 14 for induction of an immune response against VZV, wherein said composition is administered once per 5 years, more suitably once per year.
17. A composition according to any preceding claim for use in preventing VZV infection.
18. A composition according to any of claims 1 to 17 for use in prevention of shingles.
19. A composition according to any preceding claim for use in preventing VZV infection, or for use in prevention of shingles, wherein a single dose of said composition is administered.
20. A composition according to any preceding claim for use in preventing VZV infection, or for use in prevention of shingles, wherein said composition is administered once.
21. Use of a composition according to any of claims 1 to 20 in medicine.

22. Use of a composition according to any of claims 1 to 20 in the preparation of a medicament for prevention of VZV infection.
23. Use of a composition according to any of claims 1 to 20 in the preparation of a medicament for prevention of shingles.
24. Use of a composition according to any of claims 1 to 20 in the preparation of a medicament for induction of, or that induces, both CD4+ and CD8+ T cell responses to Gly E antigen in a subject.
25. Use according to claim 24 wherein said medicament further induces antibodies to Gly E antigen in said subject.
26. A method of inducing an immune response against varicella-zoster virus (VZV) in a mammalian subject, the method comprising administering a composition according to any of claims 1 to 20 to said subject.
27. A method of preventing shingles in a mammalian subject, the method comprising administering a composition according to any of claims 1 to 20 to said subject.
28. A method according to claim 26 or claim 27 wherein a single dose of said composition is administered to said subject.
29. A method according to claim 26 or claim 27 wherein said composition is administered once.
30. A method according to claim 26 or claim 27 wherein said composition is administered once per 5 years, more suitably once per year.
31. A method according to any of claims 26 to 30 wherein said composition is administered by a route of administration selected from a group consisting of subcutaneous, intradermal and intramuscular.
32. A method according to claim 31 wherein said administration is intramuscular.

33. Use according to claim 22 to 25, or a method according to any of claims 26 to 31, wherein said subject is human.
- 5 34. A composition according to any of claims 1 to 17 for use in treatment or prevention of chickenpox.