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(54) **Titre : FORMULATION D'ANTICORPS MONOCLONAL ANTI-RSV**
(54) **Title: ANTI-RSV MONOCLONAL ANTIBODY FORMULATION**

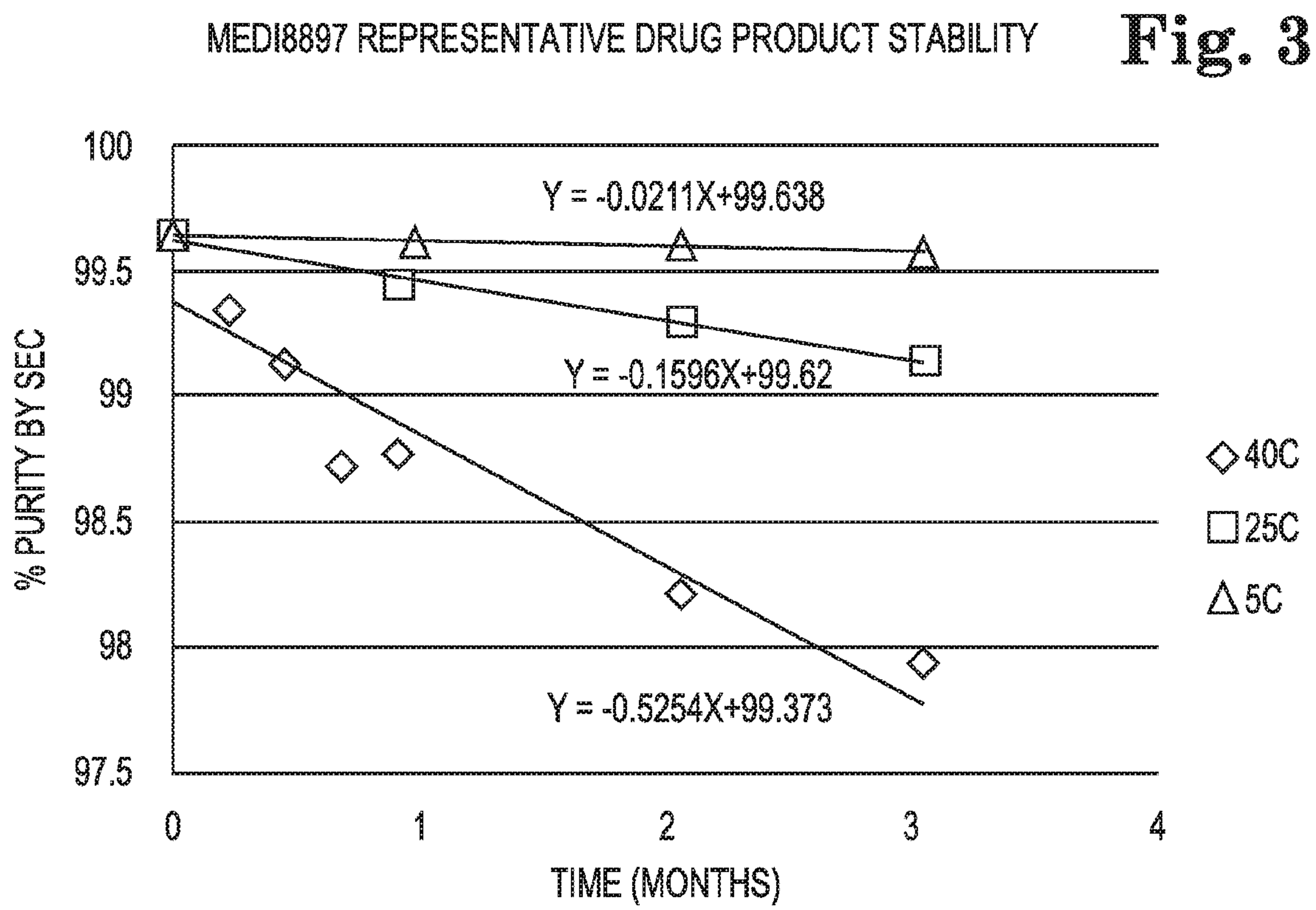

Fig. 3

(57) **Abrégé/Abstract:**
The present invention provides a formulation comprising: (i) an anti-RSV monoclonal antibody; and (ii) an ionic excipient; wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater and the ionic excipient is present at a concentration of between 50 and 150 mM and the formulation has a pH of about 5.5 to about 7.5.

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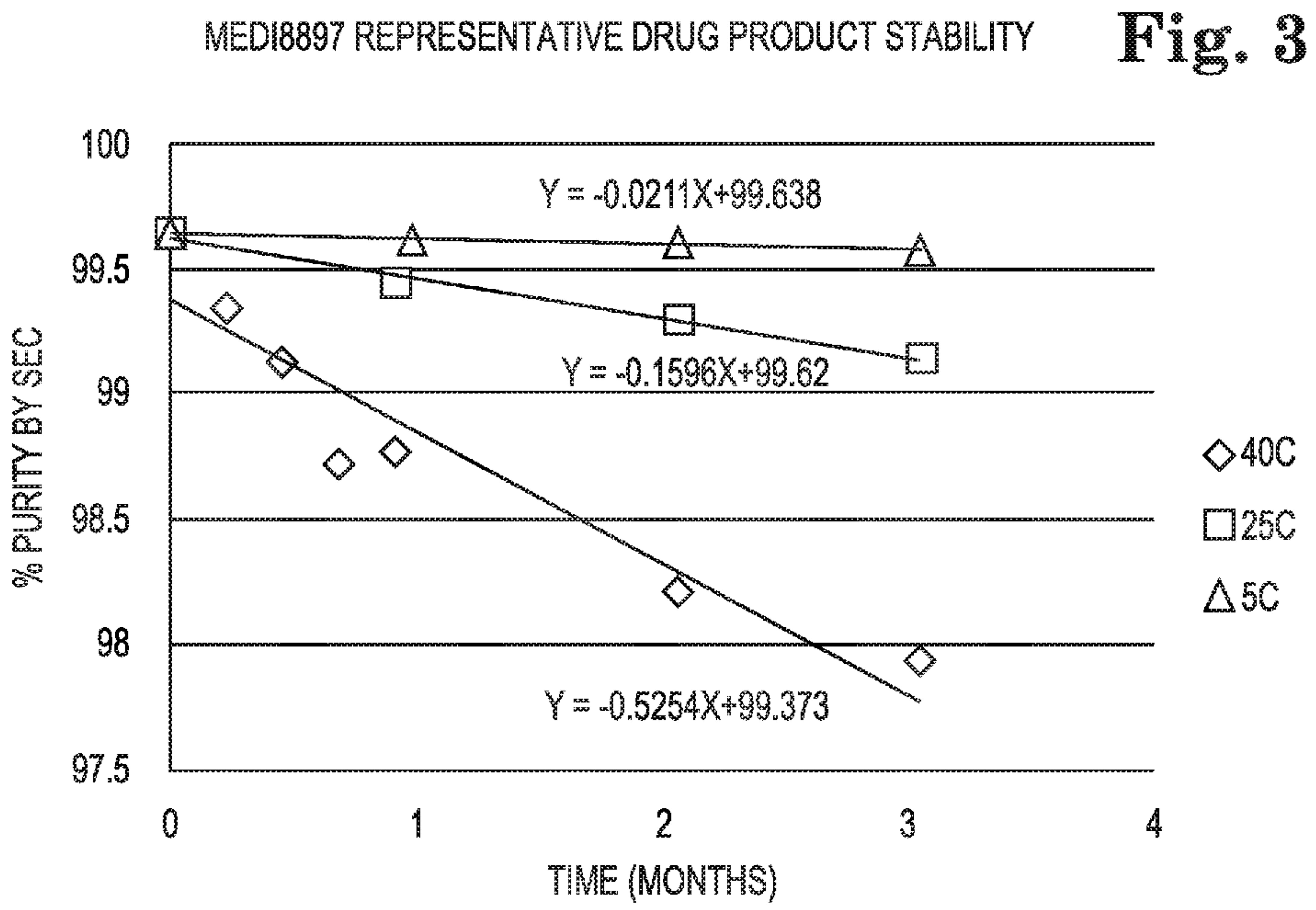
(54) Title: ANTI-RSV MONOCLONAL ANTIBODY FORMULATION

Fig. 3



(57) Abstract: The present invention provides a formulation comprising: (i) an anti-RSV monoclonal antibody; and (ii) an ionic excipient; wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater and the ionic excipient is present at a concentration of between 50 and 150 mM and the formulation has a pH of about 5.5 to about 7.5.

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ANTI-RSV MONOCLONAL ANTIBODY FORMULATION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No. 62/465,379, filed March 1, 2017, which is incorporated by reference herein.

SEQUENCE LISTING

This application contains a Sequence Listing electronically submitted via EFS-Web to the United States Patent and Trademark Office as an ASCII text file entitled "490-00050201_ST25.txt" having a size of 12 kilobytes and created on February 28, 2018. The information contained in the Sequence Listing is incorporated by reference herein.

FIELD OF THE INVENTION

The invention is concerned with an anti-RSV antibody formulation, in particular, an anti-RSV monoclonal antibody formulation and uses thereof. The invention also is concerned with an isolated anti-RSV monoclonal antibody and uses thereof.

BACKGROUND OF THE INVENTION

Respiratory Syncytial Virus (RSV) is a common cold virus belonging to the family of paramyxovirus. RSV is virulent, easily transmissible and the most common cause of lower respiratory tract disease in children of less than 2 years of age. Up to 98% of children attending day care will be infected in a single RSV season. Between 0.5%> and 3.2% of children with RSV infection require hospitalization. Approximately 90,000 hospital admissions and 4,500 deaths per year were reported in United States. Major risk factors for hospitalization due to RSV are premature birth, chronic lung disease, congenital heart disease, compromised immunity, and age younger than 6 weeks in otherwise healthy children. There is a need for additional treatment for RSV positive bronchiolitis beside supportive care in the form of adequate nutrition and oxygen therapy. Antiviral therapies such as Ribavirin have not been proven to be effective in RSV infection. One monoclonal antibody, Palivizumab (also called Synagis<®>), is registered for prophylaxis against RSV infection. Palivizumab is a genetically engineered (humanized) monoclonal antibody to the fusion protein of RSV. While Palivizumab has been a very effective prophylactic, alternative antibodies and therapies providing additional coverage against RSV would be advantageous.

As a result of the isoelectric point (pI) of a number of anti-RSV monoclonal antibodies being in the preferred pharmaceutical pH formulation range for proteins (pH 5.5 to pH 7.5), these molecules present unique formulation challenges.

Colloidal instability at a molecules pI is due to a lack of an electrostatic charge on the molecule, which allows closer protein-protein interactions (so-called "self-association") that lead to physical instabilities. For this reason, the pH of a protein formulation is typically selected to be at least 1 pH unit away from the protein pI. This aims to provide colloidal stability and thus prevent the physical instabilities, such as aggregation, precipitation, opalescence, phase separation and/or particle formation.

According to the '1 pH unit away' rule, antibodies having a low or neutral pI *e.g.* pI of pH 5.5 to pH 7.5 thus should be formulated into a formulation with a pH outside the range of 5.5 to 7.5. However, outside this range, additional instabilities can be observed. At more acidic pH, an increased rate of fragmentation reduced conformational stability and increased aggregation can be observed. At more basic pH, the potential for increased oxidation, deamidation and fragmentation and incompatibility with glass containers are present.

The above instabilities are particularly problematic in such anti-RSV antibody formulations where the antibody is present at a commercially desirable concentration *e.g.* 50mg/ml and above.

Therefore, there exists a need to provide an improved formulation for an anti-RSV antibody having a low or neutral pI. In particular, there exists a need to provide a stable formulation for an anti-RSV antibody having a low or neutral pI and, particularly such a formulation having a commercially desirable antibody concentration.

BRIEF SUMMARY OF THE INVENTION

The present invention provides a new anti-RSV antibody formulation, in particular a new anti-RSV monoclonal antibody formulation. In particular, the present formulation provides a means for improving colloidal stability for antibodies having a low or neutral pI. The present invention thus provides an alternative to the '1 pH away' rule for providing colloidal stability. The present invention thus allows antibodies having a low or neutral pI to be formulated within 1 pH unit of the antibody pI. Thus, the present invention enables such antibodies to be formulated within a pH range of 5.5 to 7.5 and at a commercially useful concentration, whilst substantially avoiding the instabilities associated with more acidic or more basic pHs.

The present invention further provides a new anti-RSV antibody MEDI8897. An improved pharmaceutically suitable formulation of the new anti-RSV antibody MEDI8897 is facilitated by formulating the antibody according to the teaching of the present invention.

The invention is particularly concerned with anti-RSV antibodies having a low or neutral pI, in particular the MEDI8897 antibody. MEDI8897 is a human IgG1κ- YTE monoclonal antibody directed against RSV-F protein.

MEDI8897 has a full length heavy chain sequence of Figure 1 (SEQ ID NO: 2) and a full length light chain sequence of Figure 2 (SEQ ID NO: 1).

MEDI8897 has CDR sequences: light chain CDR-L1 of QASQDIVNYLN (SEQ ID NO: 3), light chain CDR-L2 of VASNLET (SEQ ID NO: 4), light chain CDR-L3 of QQYDNLPLT (SEQ ID NO: 5), heavy chain CDR-H1 of DYIIN (SEQ ID NO: 6), heavy chain CDR-H2 of GIIPVLGTVHYGPKFQG (SEQ ID NO: 7), and heavy chain CDR-H3 of ETALVVSETYLPHYFDN (SEQ ID NO: 8). The 6 CDRS are underlined in Figures 1 and 2.

MEDI8897 has a light chain variable sequence of amino acid residues 1 to 107 of Figure 1 (SEQ ID NO: 9) and a heavy chain variable sequence of amino acid residues 1 to 126 of Figure 2 (SEQ ID NO: 10).

MEDI8897 pI was measured by cIEF to be 6.4 to 6.7, with the main peak at 6.4. The pI thus overlaps with the desired pharmaceutical formulation buffer range and suggests potential issues with manufacturing, formulation and storage stability if formulated within this range.

The invention provides a formulation comprising:

i. an anti-RSV monoclonal antibody; and

ii. an ionic excipient;

wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater (e.g., about 50 mg/ml to about 200 mg/ml) and the ionic excipient is present at a concentration of about 50 to 150 mM and the formulation has a pH of about 5.5 to about 7.5.

In one embodiment, the anti-RSV monoclonal antibody has a low or neutral pI, for example in the range about pH 5.5 to about pH 7.5. In one embodiment, the monoclonal antibody has a pI in the range of about pH 6.0 to about pH 7.5. In one embodiment, the monoclonal antibody has a pI in the range of pH about 6.3 to about pH 7.5. In one embodiment, the monoclonal antibody has a pI in the range of about pH 6.4 to about pH 7.5. In one embodiment, the monoclonal antibody has a pI in the range of about pH 6.4 to about pH 6.7. In one embodiment, the monoclonal antibody has a pI of about pH 6.4. Without wishing to be bound by theory, a low to neutral pI can occur for proteins where there is a either a net balance of oppositely charged (positive amine groups and negative carboxylate groups) amino acid side chains on the protein or different domains have overall oppositely charge, within a pH range of about 5.5 to about 7.5. Again, without wishing to be bound by theory, it is possible that the ionic excipient in the formulation of the invention shields these opposing and attractive charges, thus colloidally stabilizing proteins having a pI within this range. The present invention thus provides use of an ionic excipient in an antibody formulation for the purpose of changing the charge state or distribution of the antibody in the formulation. The present invention further provides use of an ionic excipient in an antibody formulation for the purpose of colloidally stabilizing the antibody in the formulation.

In one embodiment, the monoclonal antibody is present in the formulations described herein at a concentration of about 75 mg/ml or greater (e.g., about 75 mg/ml to about 200 mg/ml). In one embodiment, the monoclonal antibody is present in the formulations described herein at a concentration of about 100 mg/ml or greater. In one embodiment, the anti-RSV monoclonal antibody is present in the formulations described herein at a concentration of about 100 mg/ml to about 165 mg/ml. In one embodiment, the anti-RSV monoclonal antibody is present at a concentration of about 100mg/ml.In one embodiment, the ionic excipient is present at a concentration of about 75 mM to about 100 mM. In one embodiment, the ionic excipient is present at a concentration of about 75 mM. In one embodiment, the ionic excipient is present at a concentration of about 80 mM.

In one embodiment, the monoclonal antibody is an IgG1 monoclonal antibody. The invention thus provides a formulation comprising:

i. an IgG1 anti-RSV monoclonal antibody; and

ii. an ionic excipient;

wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater (e.g., about 50 mg/ml to about 200 mg/ml) and the ionic excipient is present at a a concentration of about 50 to about 150 mM and the formulation has a pH of about 5.5 to about 7.5.

In one embodiment, the formulations described herein have a pH in the range of about pH 5.5 to about pH 6.5. In one embodiment, the formulations described herein have a pH in the range of about pH 5.7 to about pH 6.3. In one embodiment, the formulations described herein have a pH in the range of about pH 5.7 to about pH 6.1. Preferred formulations have a pH of about 5.8. Other preferred formulations have a pH of about 6.0.

In one embodiment, the ionic excipient is a charged amino acid. In one embodiment, the ionic excipient is lysine. In another embodiment, the ionic excipient is arginine.

In one embodiment, the ionic excipient is a salt. The invention thus provides a formulation comprising:

i. an anti-RSV monoclonal antibody as defined anywhere herein; and

ii. a salt;

wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater and the salt is present at a concentration of about 50 to about 150 mM and the formulation has a pH of about 5.5 to about 7.5.

In one embodiment, the salt is present at a concentration of about 75 mM to about 100 mM. In one embodiment, the salt is present at a concentration of about 75 mM or about 80 mM.

In one embodiment, the salt is arginine hydrochloride, for example at a concentration of about 75 mM to about 100 mM, suitably at a concentration of about 80 mM.

In one embodiment, the formulation further comprises a sugar. Amongst other known benefits, the presence of a sugar can improve tonicity of the formulation. This is desirable since preferred formulations are isotonic or near isotonic. In one embodiment, the ionic excipient is a salt and the formulation further comprises a sugar.

The invention thus provides a formulation comprising:

i. an anti-RSV monoclonal antibody as defined anywhere herein;

ii. an ionic excipient (*e.g.* a salt) as defined anywhere herein;

iii. a sugar as defined anywhere herein; and

wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater and the ionic excipient is present at a concentration of about 50 to about 150 mM and the formulation has a pH of about 5.5 to about 7.5.

In one embodiment, the formulation further comprises a sugar and the ionic excipient is present at a concentration in the range of about 75mM to less than 150 mM. In one embodiment, the formulation further comprises a sugar and the ionic excipient is present at a concentration in the range of about 75mM to about 100mM. In one embodiment, the formulation further comprises a sugar, which is present at a concentration in the range of about 100mM to about 140mM, and the ionic excipient is present at a concentration in the range of about 75mM to about 100mM.

In one embodiment, the sugar is sucrose, for example at a concentration of about 100 mM to about 140 mM, suitably at a concentration of about 120 mM.

In one embodiment, the formulation further comprises one or more buffers. In one embodiment, the one or more buffers is a buffer comprising histidine. In one embodiment, the one or more buffers are selected from a buffer comprising histidine succinate, histidine acetate, histidine citrate, histidine chloride or histidine sulfate. In one embodiment, the one or more buffers is histidine, histidine hydrochloride, or a combination thereof (histidine/ histidine hydrochloride). In one embodiment, the one or more buffers is L-histidine/ L-histidine hydrochloride monohydrate, for example at a concentration of about 10 mM to about 50 mM, suitably at a concentration of about 30 mM. It will be understood that a buffer may, itself, be an ionic excipient. Thus, in one embodiment, the buffer is the ionic excipient. In this embodiment, the concentration of the buffer should be above 50 mM i.e. in line with the concentration of the ionic excipient disclosed herein. Put another way, in one embodiment, the ionic excipient also acts as a buffer in the formulation. In this embodiment, an additional buffer may or may not be present.

In one embodiment, the formulation further comprises a surfactant. In one embodiment, the surfactant is a polysorbate, including for example, polysorbate-80.

In one embodiment, the formulation further comprises a sugar and one or more buffers. In one embodiment, the ionic excipient is a salt and the formulation further comprises a sugar and one or more buffers.

In one embodiment, the formulation further comprises a surfactant, a sugar and one or more buffers. In one embodiment, the ionic excipient is a salt and the formulation further comprises a surfactant, a sugar and one or more buffers.

The invention thus provides a formulation comprising:

i. an anti-RSV monoclonal antibody as defined anywhere herein;
ii. an ionic excipient (*e.g.* a salt) as defined anywhere herein;
iii. a sugar as defined anywhere herein;
iv. one or more buffers as defined anywhere herein; and
v. optionally a surfactant as defined anywhere herein

wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater and the ionic excipient is present at a concentration of about 50 to about 150 mM and the formulation has a pH of about 5.5 to about 7.5.

The invention also provides a formulation comprising:

i. an anti-RSV monoclonal antibody having a heavy chain variable region CDR1 sequence comprising a sequence which is at least 70% identical to the heavy chain variable region CDR1 sequence of MEDI 8897, and a heavy chain variable region CDR2 sequence comprising a sequence which is at least 70% identical to the heavy chain variable region CDR2 sequence of MEDI 8897, and a heavy chain variable region CDR3 sequence comprising a sequence which is at least 70% identical to the heavy chain variable region CDR3 sequence of MEDI 8897, and a light chain variable region CDR1 sequence comprising a sequence which is at least 70% identical to the light chain variable region CDR1 sequence of MEDI 8897, and a light chain variable region CDR2 sequence comprising a sequence which is at least 70% identical to the light chain variable region CDR2 sequence of MEDI 8897, and a light chain variable region CDR3 sequence comprising a sequence which is at least 70% identical to the light chain variable region CDR3 sequence of MEDI 8897;

ii. an ionic excipient (*e.g.* a salt) as defined anywhere herein;

iii. a sugar as defined anywhere herein;

iv. one or more buffers as defined anywhere herein; and

v. optionally a surfactant as defined anywhere herein

wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater (e.g., about 50 mg/ml to about 200 mg/ml) and the ionic excipient is present at a a concentration of about 50 to about 150 mM and the formulation has a pH of about 5.5 to about 7.5. In one embodiment, the anti-RSV monoclonal antibody has a heavy chain variable region CDR1 sequence comprising a sequence which is at least 80% identical to the heavy chain variable region CDR1 sequence of MEDI 8897, and a heavy chain variable region CDR2 sequence comprising a sequence which is at least 80% identical to the heavy chain variable region CDR2 sequence of MEDI 8897, and a heavy chain variable region CDR3 sequence comprising a sequence which is at least 80% identical to the heavy chain variable region CDR3 sequence of MEDI 8897, and a light chain variable region CDR1 sequence comprising a sequence which is at least 80% identical to the light chain variable region CDR1 sequence of MEDI 8897, and a light chain variable region CDR2 sequence comprising a sequence which is at least 80% identical to the light chain variable region CDR2 sequence of MEDI 8897, and a light chain variable region CDR3 sequence comprising a sequence which is at least 80% identical to the light chain variable region CDR3 sequence of MEDI 8897. In one embodiment, the anti-RSV monoclonal antibody has a heavy chain variable region CDR1 sequence comprising a sequence which is at least 90% identical to the heavy chain variable region CDR1 sequence of MEDI 8897, and a heavy chain variable region CDR2 sequence comprising a sequence which is at least 90% identical to the heavy chain variable region CDR2 sequence of MEDI 8897, and a heavy chain variable region CDR3 sequence comprising a sequence which is at least 90% identical to the heavy chain variable region CDR3 sequence of MEDI 8897, and a light chain variable region CDR1 sequence comprising a sequence which is at least 90% identical to the light chain variable region CDR1 sequence of MEDI 8897, and a light chain variable region CDR2 sequence comprising a sequence which is at least 90% identical to the light chain variable region CDR2 sequence of MEDI 8897, and a light chain variable region CDR3 sequence comprising a sequence which is at least 90% identical to the light chain variable region CDR3 sequence of MEDI 8897. In one embodiment, the anti-RSV monoclonal antibody has a heavy chain variable region CDR1 sequence comprising a sequence which is at least 95% identical to the heavy chain variable region CDR1 sequence of MEDI 8897, and a heavy chain variable region CDR2 sequence comprising a sequence which is at least 95% identical to the heavy chain variable region CDR2 sequence of MEDI 8897, and a heavy chain variable region CDR3 sequence comprising a sequence which is at least 95% identical to the heavy chain variable region CDR3 sequence of MEDI 8897, and a light chain variable region CDR1 sequence comprising a sequence which is at least 95% identical to the light chain variable region CDR1 sequence of MEDI 8897, and a light chain variable region CDR2 sequence comprising a sequence which is at least 95% identical to the light chain variable region CDR2 sequence of MEDI 8897, and a light chain variable region CDR3 sequence comprising a sequence which is at least 95% identical to the light chain variable region CDR3 sequence of MEDI 8897.

The invention also provides a formulation comprising:

i. an anti-RSV monoclonal antibody having a heavy chain variable region CDR1 sequence which differs by no more than 1 amino acid from the heavy chain variable region CDR1 sequence of MEDI 8897, and a heavy chain variable region CDR2 sequence which differs by no more than 1 amino acid from the heavy chain variable region CDR2 sequence of MEDI 8897, and a heavy chain variable region CDR3 sequence which differs by no more than 1 amino acid from the heavy chain variable region CDR3 sequence of MEDI 8897, and a light chain variable region CDR1 sequence which differs by no more than 1 amino acid from the light chain variable region CDR1 sequence of MEDI 8897, and a light chain variable region CDR2 which differs by no more than 1 amino acid from the light chain variable region CDR2 sequence of MEDI 8897, and a light chain variable region CDR3 sequence comprising a sequence which which differs by no more than 1 amino acid from the light chain variable region CDR3 sequence of MEDI 8897;
ii. an ionic excipient (*e.g.* a salt) as defined anywhere herein;
iii. a sugar as defined anywhere herein;
iv. one or more buffers as defined anywhere herein; and
v. optionally a surfactant as defined anywhere herein

wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater (e.g., about 50 mg/ml to about 200 mg/ml) and the ionic excipient is present at a a concentration of about 50 to about 150 mM and the formulation has a pH of about 5.5 to about 7.5.

The invention also provides a formulation comprising:

i. an anti-RSV monoclonal antibody having the 6 CDRs of MEDI 8897;
ii. an ionic excipient (*e.g.* a salt) as defined anywhere herein;
iii. a sugar as defined anywhere herein;
iv. one or more buffers as defined anywhere herein; and

v. optionally a surfactant as defined anywhere herein

wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater (e.g., about 50 mg/ml to about 200 mg/ml) and the ionic excipient is present at a concentration of about 50 to about 150 mM and the formulation has a pH of about 5.5 to about7.5.

The invention thus provides a formulation comprising:

i. an anti-RSV monoclonal antibody having the VH and VL sequences of MEDI 8897;
ii. an ionic excipient (*e.g.* a salt) as defined anywhere herein;
iii. a sugar as defined anywhere herein;
iv. one or more buffers as defined anywhere herein; and
v. optionally a surfactant as defined anywhere herein

wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater and the ionic excipient is present at a concentration of about 50 to about 150 mM and the formulation has a pH of about 5.5 to about 7.5.

The invention thus provides a formulation comprising:

i. an anti-RSV monoclonal antibody having the full length heavy and light chain sequences of MEDI 8897;
ii. an ionic excipient (*e.g.* a salt) as defined anywhere herein;
iii. a sugar as defined anywhere herein;
iv. one or more buffers as defined anywhere herein; and
v. optionally a surfactant as defined anywhere herein

wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater (e.g., about 50 mg/ml to about 200 mg/ml) and the ionic excipient is present at a concentration of about 50 to about 150 mM and the formulation has a pH of about 5.5 to about 7.5.

The invention thus provides a formulation comprising:

i. anti-RSV monoclonal antibody MEDI 8897;
ii. an ionic excipient (*e.g.* a salt) as defined anywhere herein;
iii. a sugar as defined anywhere herein;
iv. one or more buffers as defined anywhere herein; and

v. optionally a surfactant as defined anywhere herein

wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater (e.g., about 50 mg/ml to about 200 mg/ml) and the ionic excipient is present at a concentration of about 50 to about 150 mM and the formulation has a pH of about 5.5 to about 7.5.

The invention provides a formulation comprising:

i. an anti-RSV monoclonal antibody;

ii. arginine hydrochloride;

iii. sucrose;

iv. L-histidine/ L-histidine hydrochloride monohydrate; and

v. polysorbate-80

wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater (e.g., about 50 mg/ml to about 200 mg/ml) and the arginine hydrochloride is present at a concentration of about 50 to about 150 mM and the formulation has a pH of about 5.5 to about7.5. In one embodiment, the RSV monoclonal antibody has the 6 CDRs of MEDI 8897. In one embodiment, the RSV monoclonal antibody has the VH and VL sequences of MEDI 8897. In one embodiment, the RSV monoclonal antibody has the full length heavy and light chain sequences of MEDI 8897. In one embodiment, the RSV monoclonal antibody is MEDI 8897.

The invention provides a formulation comprising:

i. an anti-RSV monoclonal antibody;

ii. arginine hydrochloride;

iii. sucrose;

iv. L-histidine/ L-histidine hydrochloride monohydrate; and

v. polysorbate-80

wherein the monoclonal antibody is present at a concentration of about 100mg/mL and the arginine hydrochloride is present at a concentration of about 80 mM and the formulation has a pH of about 6.0. The sucrose preferably has a concentration of about 120 mM. The L-histidine/ L-histidine hydrochloride monohydrate preferably has a concentration of about 30 mM. The polysorbate preferably has a concentration of between 0.02% and 0.04 %, more preferably the concentration is 0.02%. In one embodiment, the RSV monoclonal antibody has the 6 CDRs of MEDI 8897. In one embodiment, the RSV monoclonal antibody has the VH and VL sequences of MEDI 8897. In one embodiment, the RSV monoclonal antibody has the full length heavy and light chain sequences of MEDI 8897. In one embodiment, the RSV monoclonal antibody is MEDI 8897.

The formulations described herein can also include one or more additional excipients, including for example, one or more sugars, salts, amino acids, polyols, chelating agents, emulsifiers and/or preservatives.

The formulations of the invention preferably are pharmaceutical formulations.

The present invention provides an isolated monoclonal antibody having light chain CDR sequences: CDR-L1 of SEQ ID NO: 3, CDR-L2 of SEQ ID NO: 4, CDR-L3 of SEQ ID NO: 5 and heavy chain CDR sequences: CDR-H1 of SEQ ID NO: 6, CDR-H2 of SEQ ID NO: 7, CDR-H3 of SEQ ID NO: 8. The present invention provides an isolated monoclonal antibody having a light chain variable region sequence of SEQ ID NO: 9 and a heavy chain variable region sequence of SEQ ID NO: 10. The present invention provides an isolated monoclonal antibody having the three CDRs of light chain variable region of sequence of SEQ ID NO: 9 and the three CDRs of heavy chain variable region sequence of SEQ ID NO: 10. The present invention provides an isolated monoclonal antibody having a light chain sequence of SEQ ID NO: 1 and a heavy chain sequence of SEQ ID NO: 2. Preferably, the antibody is an IgG1 antibody. The present invention provides novel and inventive monoclonal antibodies *per se* based on novel and inventive monoclonal antibody MEDI-8897 as disclosed herein. The present invention provides a hybridoma capable of expressing an isolated monoclonal antibody according to the present invention. The present invention provides a nucleic acid encoding an isolated monoclonal antibody according to the present invention. The present invention provides an expression vector comprising a nucleic acid according to the present invention. The present invention provides a host cell comprising an expression vector according to the present invention. The present invention provides a process for recombinantly producing an isolated monoclonal antibody according to the present invention comprising culturing the host cell under conditions such that the antibody is expressed. The present invention provides an isolated monoclonal antibody as defined herein for use as a medicament. The present invention provides an isolated monoclonal antibody as defined herein for use in the treatment of a disease. The present invention provides a method of treating a disease in a subject comprising administering an isolated monoclonal antibody as defined herein to the subject. The present invention provides a pharmaceutical composition comprising an isolated monoclonal antibody as defined herein. The present invention provides a pharmaceutical composition as defined herein for use as a medicament. The present invention provides a pharmaceutical composition as defined herein for use in the treatment of a disease. The present invention provides a method of treating a disease in a subject comprising administering a pharmaceutical composition as defined herein to the subject.

The present invention provides a pharmaceutical formulation as described anywhere herein for use as a medicament.

The present invention provides a pharmaceutical formulation as described anywhere herein for use in the treatment or prevention of a disease.

The present invention provides a method of treating or preventing a disease in a subject comprising administering a pharmaceutical formulation as described anywhere herein to the subject. Also provided herein are methods of treating or preventing a disease in a subject by administering a therapeutically effective amount of a pharmaceutical formulation as described anywhere herein to the subject.

In one embodiment, the subject is a human. In one embodiment, the subject is a human under 2 years of age. In one embodiment, the subject is a premature baby under 6 weeks of age.

In one embodiment, the disease is a lower respiratory tract disease.

In one embodiment, the disease is RSV infection.

BRIEF DESCRIPTIONS OF THE DRAWINGS

FIG. 1 shows the MEDI8897 heavy chain nucleotide sequence and translation.

FIG. 2 shows the MEDI8897 light chain nucleotide sequence and translation.

FIG. 3 shows MEDI8897 formulation stability over a 3 month period at 5°C, 25°C and 40°C.

DETAILED DESCRIPTION OF THE INVENTION

Due to the fact that a number of monoclonal antibodies possess a pI that is close to physiologic pH, *i.e.* the pH generally desired for human administration, difficulties in formulating these monoclonal antibodies occur. For such monoclonal antibodies, for the first time, the present invention provides motivation to formulate these ‘difficult’ antibodies as pharmaceuticals. Prior to the present invention, such antibodies might have been dismissed from being considered as drug candidates because of the lack of an appropriate formulation strategy for formulating at a commercially useful concentration and within a commercially useful pH range.

The present invention provides a new monoclonal antibody formulation. Suitably, the formulation has a pH that is within 1.0 pH unit below the isoelectric point of the monoclonal antibody.

The invention provides a formulation comprising: (i) an anti-RSV monoclonal antibody; and (ii) an ionic excipient (*e.g.* a salt); wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater and the ionic excipient is present at a concentration of between 50 and 150 mM and the formulation has a pH of about 5.5 to about 7.5.

The invention further provides a formulation comprising: (i) an anti-RSV monoclonal antibody; and (ii) an ionic excipient (*e.g.* a salt); wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater (e.g., about 50 mg/ml to about 200 mg/ml) and the ionic excipient is present at a a concentration of about 50 to about 150 mM and the formulation has a pH of about 5.5 to about 7.5; and wherein the aggregation rate of the monoclonal antibody in the formulation is reduced compared to the aggregation rate of the same antibody in the same formulation but without an ionic excipient.

Aggregation rate can be measured according to standard techniques as described herein. Surprisingly, formulations in accordance with the present invention have been shown to have good stability and to have decreased self-aggregation *e.g.* to exhibit ≤ 2.0 % aggregation when stored at room temperature for 3 months. The present invention thus provides the use of an ionic excipient in an antibody formulation for the purpose of increasing stability of the antibody in the formulation. The present invention further provides the use of an ionic excipient in an antibody formulation for the purpose of decreasing self-aggregation of the antibody in the formulation.

Antibody

The formulations of the present invention are particularly useful for anti-RSV antibodies having a low or neutral pI, for example in the range about pH 5.5 to about pH 7.5, about pH 6.0 to about pH 7.5, about pH 6.3 to about pH 7.5, or about pH 6.4 to about pH 7.5. The pI of an antibody can be measured according to standard techniques, for example by capillary isoelectric focusing (cIEF). The invention thus provides a formulation comprising: (i) a monoclonal antibody having a low or neutral pI; and (ii) an ionic excipient; wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater (e.g., about 50 mg/ml to about 200 mg/ml) and the ionic excipient is present at a a concentration of about 50 to about 150 mM and the formulation has a pH of about 5.5 to about 7.5. The invention thus further provides a formulation comprising: (i) a monoclonal antibody having a low or neutral pI; and (ii) an ionic excipient; wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater and the ionic excipient is present at a a concentration of about 50 to about 150 mM and the formulation has a pH of about 5.5 to about 7.5; and wherein the aggregation rate of the monoclonal antibody in the formulation is reduced compared to the aggregation rate of the same antibody in the same formulation but without an ionic excipient.

In one embodiment, the monoclonal antibody has a pI in the range of pH 6.4 to pH 7.5.

In one embodiment, the monoclonal antibody is an IgG1 or IgG4 monoclonal antibody. Most preferably, the monoclonal antibody is an IgG1 monoclonal antibody. The invention thus provides a formulation comprising: (i) an IgG1 monoclonal anti-RSV antibody having a low or neutral pI; and (ii) an ionic excipient; wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater (e.g., about 50 mg/ml to about 200 mg/ml) and the ionic excipient is present at a a concentration of about 50 to about 150 mM and the formulation has a pH of about 5.5 to about 7.5. The invention thus further provides a formulation comprising: (i) an IgG1 monoclonal antibody having a low or neutral pI; and (ii) an ionic excipient; wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater (e.g., about 50 mg/ml to about 200 mg/ml) and the ionic excipient is present at a a concentration of about 50 to about 150 mM and the formulation has a pH of about 5.5 to about 7.5; and wherein the aggregation rate of the monoclonal antibody in the formulation is reduced compared to the aggregation rate of the same antibody in the same formulation but without an ionic excipient.

The invention is particularly concerned with formulations comprising antibody MEDI-8897 or variants thereof. In one embodiment, the anti-RSV monoclonal antibody has a heavy chain variable region CDR1 sequence comprising a sequence which is at least 70% identical to the heavy chain variable region CDR1 sequence of MEDI 8897, and a heavy chain variable region CDR2 sequence comprising a sequence which is at least 70% identical to the heavy chain variable region CDR2 sequence of MEDI 8897, and a heavy chain variable region CDR3 sequence comprising a sequence which is at least 70% identical to the heavy chain variable region CDR3 sequence of MEDI 8897, and a light chain variable region CDR1 sequence comprising a sequence which is at least 70% identical to the light chain variable region CDR1 sequence of MEDI 8897, and a light chain variable region CDR2 sequence comprising a sequence which is at least 70% identical to the light chain variable region CDR2 sequence of MEDI 8897, and a light chain variable region CDR3 sequence comprising a sequence which is at least 70% identical to the light chain variable region CDR3 sequence of MEDI 8897.

In another embodiment, the anti-RSV monoclonal antibody has a heavy chain variable region CDR1 sequence comprising a sequence which is at least 80% identical to the heavy chain variable region CDR1 sequence of MEDI 8897, and a heavy chain variable region CDR2 sequence comprising a sequence which is at least 80% identical to the heavy chain variable region CDR2 sequence of MEDI 8897, and a heavy chain variable region CDR3 sequence comprising a sequence which is at least 80% identical to the heavy chain variable region CDR3 sequence of MEDI 8897, and a light chain variable region CDR1 sequence comprising a sequence which is at least 80% identical to the light chain variable region CDR1 sequence of MEDI 8897, and a light chain variable region CDR2 sequence comprising a sequence which is at least 80% identical to the light chain variable region CDR2 sequence of MEDI 8897, and a light chain variable region

CDR3 sequence comprising a sequence which is at least 80% identical to the light chain variable region CDR3 sequence of MEDI 8897.

In one embodiment, the anti-RSV monoclonal antibody has a heavy chain variable region CDR1 sequence comprising a sequence which is at least 90% identical to the heavy chain variable region CDR1 sequence of MEDI 8897, and a heavy chain variable region CDR2 sequence comprising a sequence which is at least 90% identical to the heavy chain variable region CDR2 sequence of MEDI 8897, and a heavy chain variable region CDR3 sequence comprising a sequence which is at least 90% identical to the heavy chain variable region CDR3 sequence of MEDI 8897, and a light chain variable region CDR1 sequence comprising a sequence which is at least 90% identical to the light chain variable region CDR1 sequence of MEDI 8897, and a light chain variable region CDR2 sequence comprising a sequence which is at least 90% identical to the light chain variable region CDR2 sequence of MEDI 8897, and a light chain variable region CDR3 sequence comprising a sequence which is at least 90% identical to the light chain variable region CDR3 sequence of MEDI 8897.

In one embodiment, the anti-RSV monoclonal antibody has a heavy chain variable region CDR1 sequence comprising a sequence which is at least 95% identical to the heavy chain variable region CDR1 sequence of MEDI 8897, and a heavy chain variable region CDR2 sequence comprising a sequence which is at least 95% identical to the heavy chain variable region CDR2 sequence of MEDI 8897, and a heavy chain variable region CDR3 sequence comprising a sequence which is at least 95% identical to the heavy chain variable region CDR3 sequence of MEDI 8897, and a light chain variable region CDR1 sequence comprising a sequence which is at least 95% identical to the light chain variable region CDR1 sequence of MEDI 8897, and a light chain variable region CDR2 sequence comprising a sequence which is at least 95% identical to the light chain variable region CDR2 sequence of MEDI 8897, and a light chain variable region CDR3 sequence comprising a sequence which is at least 95% identical to the light chain variable region CDR3 sequence of MEDI 8897.

In another embodiment, the anti-RSV monoclonal antibody has a heavy chain variable region CDR1 sequence which differs by no more than 1 amino acid from the heavy chain variable region CDR1 sequence of MEDI 8897, and a heavy chain variable region CDR2 sequence which differs by no more than 1 amino acid from the heavy chain variable region CDR2 sequence of MEDI 8897, and a heavy chain variable region CDR3 sequence which differs by no more than 1 amino acid from the heavy chain variable region CDR3 sequence of MEDI 8897, and a light chain variable region CDR1 sequence which differs by no more than 1 amino acid from the light chain variable region CDR1 sequence of MEDI 8897, and a light chain variable region CDR2 which differs by no more than 1 amino acid from the light chain variable region CDR2 sequence of MEDI 8897, and a light chain variable region CDR3 sequence comprising a sequence which which differs by no more than 1 amino acid from the light chain variable region CDR3 sequence of MEDI 8897.

In another embodiment, the anti-RSV monoclonal antibody has the 6 CDRs of MEDI 8897.

In another embodiment, the anti-RSV monoclonal antibody has the 6 CDRs of MEDI 8897 in combination with 70% identity to the framework region sequences of MEDI 8897.

In another embodiment, the anti-RSV monoclonal antibody has the 6 CDRs of MEDI 8897 in combination with 80% identity to the framework region sequences of MEDI 8897.

In another embodiment, the anti-RSV monoclonal antibody has the 6 CDRs of MEDI 8897 in combination with 90% identity to the framework region sequences of MEDI 8897.

In another embodiment, the anti-RSV monoclonal antibody has the 6 CDRs of MEDI 8897 in combination with 95% identity to the framework region sequences of MEDI 8897.

In one embodiment, the anti-RSV monoclonal antibody has the 6 CDRs of MEDI 8897 in combination with the changes to the heavy chain region of MEDI 8897 selected from those shown below in Table 1:

Position Relative to SEQ ID NO. 2	Amino Acid
28	P
30	R

31	N
37	L
61	A
81	I
82	H
84	I
106	T

In one embodiment, the anti-RSV monoclonal antibody has the 6 CDRs of MEDI 8897 in combination with the changes to the heavy chain region of MEDI 8897 selected from those shown below in Table 2:

Position Relative to SEQ ID NO. 2	Amino Acid
28	P
30	R
31	N
61	A
106	T

In one embodiment, the anti-RSV monoclonal antibody has the 6 CDRs of MEDI 8897 in combination with the changes to the heavy chain region of MEDI 8897 selected from those shown below in Table 3:

Position Relative to SEQ ID NO. 2	Amino Acid
28	P
30	R
31	N
45	L
61	A
106	T

In one embodiment, the anti-RSV monoclonal antibody has the 6 CDRs of MEDI 8897 in combination with the changes to the heavy chain region of MEDI 8897 selected from those shown below in Table 4:

Position Relative to SEQ ID NO. 2	Amino Acid
19	K
23	K
28	T
29	F
30	S
31	N
45	L
61	A
106	T

In one embodiment, the anti-RSV monoclonal antibody has the 6 CDRs of MEDI 8897 in combination with the changes to the heavy chain region of MEDI 8897 selected from those shown below in Table 5:

Position Relative to SEQ ID NO. 2	Amino Acid
28	P
106	T

In one embodiment, the anti-RSV monoclonal antibody has the 6 CDRs of MEDI 8897 in combination with the changes to the heavy chain region of MEDI 8897 selected from those shown below in Table 6:

Position Relative to SEQ ID NO. 2	Amino Acid
28	P
106	T
109	R

In one embodiment, the anti-RSV monoclonal antibody has the 6 CDRs of MEDI 8897 in combination with the changes to the heavy chain region of MEDI 8897 selected from those shown below in Table 7:

Position Relative to SEQ ID NO. 2	Amino Acid
19	K
23	K
77	S
82	H
98	R
106	T

In one embodiment, the anti-RSV monoclonal antibody has the 6 CDRs of MEDI 8897 in combination with the changes to the heavy chain region of MEDI 8897 selected from those shown below in Table 8:

Position Relative to SEQ ID NO. 2	Amino Acid
19	K
23	K
82	H
106	T

In one embodiment, the anti-RSV monoclonal antibody has the 6 CDRs of MEDI 8897 in combination with the changes to the heavy chain region of MEDI 8897 selected from those shown below in Table 9:

Position Relative to SEQ ID NO. 2	Amino Acid
19	K
23	K
77	S
106	T

In one embodiment, the anti-RSV monoclonal antibody has the 6 CDRs of MEDI 8897 in combination with the changes to the heavy chain region of MEDI 8897 selected from those shown below in Table 10:

Position Relative to SEQ ID NO. 2	Amino Acid
19	K
23	K
77	S
82	H
106	T

In another embodiment, the anti-RSV monoclonal antibody has the VH and VL sequences of MEDI 8897.

Preferably, the antibody is an IgG1 antibody.

Preferably, the anti-RSV monoclonal antibody defined anywhere herein has a heavy chain variable region CDR3 sequence ETALVVSETYLPHYFDN (SEQ ID NO: 8).

In one embodiment of the anti-RSV monoclonal antibody defined anywhere herein, the CDR3 of the heavy chain does not comprise the sequence ETALVVSTTYLPHYFDN. Preferably, any variant heavy chain variable region CDR3 sequences (i.e variants of SEQ ID NO: 8) in the anti-RSV monoclonal antibody defined anywhere herein retain E at the position marked by *: ETALVVS*TYLPHYFDN. Preferably, any variant heavy chain variable region CDR3 sequences (i.e variants of SEQ

ID NO: 8) in the anti-RSV monoclonal antibody defined anywhere herein do not have T at the position marked by *: ETALVVS*TYLPHYFDN.

In an embodiment the anti-RSV monoclonal antibody has a modified Fc region wherein one or more amino acids has been inserted, deleted or substituted so as to increase the half-life of the antibody. In an embodiment, the anti-RSV monoclonal antibody has three amino acid substitutions (M252Y/S254T/T256E; called YTE) in the CH2 region of the Fc domain.

In another embodiment, the anti-RSV monoclonal antibody has the full length heavy and light chain sequences of MEDI 8897. Anti-RSV antibodies include antibody functional parts, e.g., antibodies or antigen-binding fragments, variants, or derivatives thereof. Anti-RSV antibodies further include, but are not limited to, polyclonal, monoclonal, human, humanized, or chimeric antibodies, single chain antibodies, bispecific antibodies, epitope-binding fragments, e.g., Fab, Fab' and F(ab')2, Fd, Fvs, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv), fragments comprising either a VL or VH domain, fragments produced by a Fab expression library. ScFv molecules are known in the art and are described, e.g., in US patent 5,892,019. Immunoglobulin or antibody molecules encompassed by this disclosure can be of any type (e.g., IgG, IgE, IgM, IgD, IgA, and IgY), class (e.g., IgGl, IgG2, IgG3, IgG4, IgAl and IgA2) or subclass of immunoglobulin molecule.

Antibody Concentration

Suitably, the monoclonal antibody is present in the formulations described herein at a concentration of about 50 mg/ml to about 300 mg/ml, about 50 mg/ml to about 200 mg/ml, about 100 mg/ml to about 200 mg/ml, about 100 mg/ml to about 165 mg/ml, about 100 mg/ml to about 150 mg/ml, or about 50 mg/ml, about 75 mg/ml, about 100 mg/ml, about 105 mg/ml, about 110 mg/ml, about 115 mg/ml, about 120 mg/ml, about 125 mg/ml, about 130 mg/ml, about 135 mg/ml, about 140 mg/ml, about 145 mg/ml, about 150 mg/ml, about 155 mg/ml, about 160 mg/ml, about 165 mg/ml, about 170 mg/ml, about 175 mg/ml, about 180 mg/ml, about 185 mg/ml, about 190 mg/ml, about 195 mg/ml, or about 200 mg/ml, including values and ranges within these ranges.

Suitably, the monoclonal antibody is present in the formulations described herein at a concentration of about 100 mg/ml to about 165 mg/ml. Suitably, the monoclonal antibody is present in the formulations described herein at a concentration of about 100 mg/ml.

pH

Suitably, the formulations described herein have a pH in the range of about pH 5.5 to about pH 6.5 in order to provide near optimal or optimal chemical stability (hydrolysis, deamidation, isomerization). In one embodiment, the formulations described herein have a pH in the range of about pH 5.7 to about pH 6.3. In one embodiment, the formulations described herein have a pH in the range of about pH 5.7 to about pH 6.1. Preferred formulations have a pH of about 5.8. Other preferred formulations have a pH of about 6.0.

Suitably, the formulations described herein have a pH in the range of about pH 5.5 to about pH 6.0, about pH 5.7 to about pH 6.0, or about pH 5.5, about pH 5.6, about pH 5.7, about pH 5.8, about pH 5.9, about pH 6.0, about pH 6.1, about pH 6.2, about pH 6.3, about pH 6.4, or about pH 6.5. In embodiments, the pH of the formulations provided herein is 5.7 to 6.0, more suitably the formulations have a pH of about 5.8.

A formulation pH close to about pH 7.4 also can be desirable for injection site tolerability.

Ionic Excipient

Exemplary ionic excipients for use in the formulations include salts and charged amino acids. The ionic excipient might comprise a combination of a salt and charged amino acid.

Exemplary charged amino acids include arginine and lysine.

Exemplary salts include salts of charged amino acids, for example, succinate, acetate, and sulfate salts of arginine and lysine.

Further, exemplary salts are those described herein including, but not limited to, sodium chloride, as well as other salts with sodium, potassium, calcium, magnesium and the like, such as chlorides, carbonates, sulphates, acetates, gluconates, lactates, malates, and other auxiliaries and the like which are customary in the field of parenteral administration. Suitably the salt is selected from sodium chloride (NaCl), lysine hydrochloride and arginine hydrochloride. In one embodiment, the salt is NaCl. In another embodiment, the salt is arginine hydrochloride.

The concentration of the ionic excipient, suitably salt, in the pharmaceutical formulations described herein is generally in the range of about 50 mM to about 300 mM, more suitably about 50 mM to about 200 mM, about 50 mM to about 150 mM, about 50 mM to about 100 mM, about 60 mM to about 80 mM, or about 50 mM, about 55 mM, about 60 mM, about 65 mM, about 70 mM, about 75 mM, about 80 mM, about 85 mM, about 90 mM, about 95 mM or about 100 mM, including any ranges or values within these ranges.In one embodiment, the ionic excipient is present at a concentration of about 50 mM to about 125 mM.

In one embodiment, the ionic excipient is present at a concentration of about 50 mM to about 100 mM.

In one embodiment, the ionic excipient is present at a concentration of about 75 mM to about 100 mM.

In suitable embodiments, the salt is NaCl, for example at a concentration of about 50 mM to about 100 mM, suitably at a concentration of about 70 mM.

In suitable embodiments, the salt is arginine hydrochloride, for example at a concentration of about 50 mM to about 100 mM, suitably at a concentration of about 80 mM.

Buffers

The formulations described herein suitably comprise one or more buffers. As used herein, “buffer” refers to an excipient for maintaining the pH of a formulation. Exemplary buffers for use in the formulations provided herein include, but are not limited to histidine, histidine hydrochloride (histidine HCl), sodium succinate, sodium acetate, sodium acetate/acetic acid, sodium phosphate, citrate, phosphate, succinate, glycine, and acetate. In one embodiment, the buffer for use in the formulations described herein is sodium acetate/acetic acid. In one embodiment, the one or more buffers is a buffer comprising histidine. In one embodiment, the one or more buffers are selected from a buffer comprising histidine succinate, histidine acetate, histidine citrate, histidine chloride or histidine sulfate. In one embodiment, the one or more buffers is histidine, histidine hydrochloride, or a combination thereof (histidine/ histidine hydrochloride). In one embodiment, the one or more buffers is L-histidine/ L-histidine hydrochloride monohydrate.

The concentration of a buffer, suitably sodium acetate/acetic acid, in the pharmaceutical formulations described herein is generally in the range of about 10 mM to about 100 mM, more suitably about 15 mM to about 80 mM, about 25 mM to about 75 mM, about 30 mM to about 60 mM, about 40 mM to about 60 mM, about 40 mM to about 50 mM, or about 15 mM, about 20 mM, about 25 mM, about 30 mM, about 35 mM, about 40 mM, about 45 mM, about 50 mM, about 55 mM, about 60 mM, about 65 mM, about 70 mM or about 75 mM, including any ranges or values within these ranges.

In one embodiment, the one or more buffers is L-histidine/ L-histidine hydrochloride monohydrate, for example at a concentration of about 10 mM to about 50 mM, suitably at a concentration of about 30 mM.

The pH of the buffer is preferably in the range of pH5.5 to pH6.0.

It will be understood that a buffer may, itself, be an ionic excipient. Thus, in one embodiment, the buffer is the ionic excipient. In this embodiment, the concentration of the buffer should be above 50 mM i.e. in line with the concentration of the ionic excipient disclosed herein. Preferable concentrations for the buffer in this embodiment are as discussed anywhere herein in relation to the ionic excipient.

Put another way, in one embodiment, the ionic excipient also acts as a buffer in the formulation. In this embodiment, an additional buffer may or may not be present.

Sugars and Surfactants

The formulations described herein suitably comprise a sugar, for example, but not limited to, trehalose, lactose, mannitol, melibiose, melezitose, raffinose, mannotriose, stachyose and sucrose. In other embodiments, a polyol such as trihydric or higher molecular weight sugar alcohols, e.g. glycerin, dextran, erythritol, glycerol, arabitol, xylitol, sorbitol, and mannitol, can be used. Examples of reducing sugars include, but are not limited to, glucose, maltose, maltulose, iso-maltulose and lactulose. Examples of non-reducing sugars include, but are not limited to, trehalose, non-reducing glycosides of polyhydroxy compounds selected from sugar alcohols and other straight chain polyalcohols. Examples of sugar alcohols include, but are not limited to, monoglycosides, compounds obtained by reduction of disaccharides such as lactose, maltose, lactulose and maltulose. The glycosidic side group can be either glucosidic or galactosidic. Additional examples of sugar alcohols include, but are not limited to, glucitol, maltitol, lactitol and iso-maltulose. In one embodiment, the sugar is selected from the group consisting of trehalose, lactose, mannitol, raffinose and sucrose. In specific embodiments, trehalose is used as a sugar in the formulations described herein. In specific embodiments, sucrose is used as a sugar in the formulations described herein.

Suitably, the amount of sugar, for example trehalose, in a formulation described herein is about 1 % (w/v) to about 10 % (w/v). Unless otherwise noted, percentage of a component (%) is used herein indicate a weight/volume (w/v) %. In exemplary embodiments, the amount of sugar in a pharmaceutical formulation described herein is about 1 % (w/v) to about 8 % (w/v), or about 2 % (w/v) to about 6 % (w/v), about 2 % (w/v) to about 5 % (w/v), about 3 % (w/v) to about 5 % (w/v), or about 1 % (w/v), about 2 % (w/v), about 3 % (w/v), about 4 % (w/v), about 5 % (w/v), about 6 % (w/v), about 7 % (w/v), about 8 % (w/v), about 9 % (w/v), or about 10 % (w/v), including any values and ranges within these ranges.

The formulations described herein suitably comprise a surfactant.

The term “surfactant” as used herein refers to organic substances having amphipathic structures; namely, they are composed of groups of opposing solubility tendencies, typically an oil- soluble hydrocarbon chain and a water-soluble ionic group. Surfactants can be classified, depending on the charge of the surface-active moiety, into anionic, cationic, and nonionic surfactants. Surfactants are often used as wetting, emulsifying, solubilizing, and dispersing agents for various pharmaceutical formulations and preparations of biological materials. Pharmaceutically acceptable surfactants like polysorbates (e.g. polysorbates 20, 40, 60 or 80); polyoxamers (e.g. poloxamer 188); Triton; sodium octyl glycoside; lauryl-, myristyl-, linoleyl- , or stearyl-sulfobetaine; lauryl-, myristyl-, linoleyl- or stearyl-sarcosine; linoleyl-, myristyl-, or cetyl-betaine; lauroamidopropyl-, cocamidopropyl-, linoleamidopropyl-, myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-betaine (e.g. lauroamidopropyl); myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-dimethylamine; sodium methyl cocoyl-, or disodium methyl oleyl-taurate; and the MONAQUA™ series (Mona Industries, Inc., Paterson, N. J.), polyethyl glycol, polypropyl glycol, and copolymers of ethylene and propylene glycol (e.g. Pluronics, PF68 etc), can be used in the pharmaceutical formulations described herein. Suitably the surfactant is a polysorbate, including for example, polysorbate-20, polysorbate-40, polysorbate-60, and polysorbate-80. In one embodiment, the surfactant is polysorbate-80.

Suitably, the formulations described herein comprise a surfactant (suitably polysorbate-80) at about 0.001 % to about 0.5 % (w/v), more suitably about 0.002 % to about 0.1 % of a surfactant, for example about 0.01 % to about 0.2 %, about 0.02 % to about 0.1 %, about 0.02 % to about 0.07 %, about 0.03 % to about 0.06 %, about 0.04 % to about 0.06 %, or about 0.02 %, about 0.025 %, about 0.03 %, about 0.035 %, about 0.04 %, about 0.045 %, about 0.05 %, about 0.055 %, about 0.060 %, about 0.065 %, about 0.07 %, about 0.075 %, about 0.08 %, about 0.085 %, about 0.09 %, about 0.095 %, or about 0.1% of a surfactant, including any ranges or values within these ranges.

The formulations described herein suitably comprise a surfactant and a sugar. The formulations described herein suitably comprise a surfactant and one or more buffers. The formulations described herein suitably comprise a sugar and one or more buffers. The formulations described herein suitably comprise a surfactant, a sugar, and one or more buffers.

The formulations described herein can also include one or more additional excipients, including for example, one or more sugars, salts, amino acids, polyols, chelating agents, emulsifiers and/or preservatives.

Pharmaceutical Use

The formulations of the invention preferably are pharmaceutical formulations. Suitably, the pharmaceutical formulations described herein are “pharmaceutically acceptable,” and thus would meet the necessary approval requirements required by a regulatory agency of the Federal or a state government, or listed in the U.S.

Pharmacopeia, European Pharmacopeia, or other generally recognized pharmacopeia, so as to be used in animals, and more particularly in humans.

The present invention provides a pharmaceutical formulation as described anywhere herein for use as a medicament. The present invention provides a pharmaceutical formulation as described anywhere herein for use in the treatment of a disease. The present invention provides a method of treating a disease in a subject comprising administering a pharmaceutical formulation as described anywhere herein to the subject. Also provided herein are methods of treating a subject by administering a therapeutically effective amount of a pharmaceutical formulation as described anywhere herein to the subject.

As used herein, the term “subject” includes any human or nonhuman animal. The term “nonhuman animal” includes all vertebrates, for example, but not limited to, mammals and non-mammals, such as nonhuman primates, sheep, dogs, cats, horses, cows, chickens, amphibians, reptiles, etc. In one embodiment, the subject is a human.

The present invention provides a method of treating or preventing a disease in a subject comprising administering a pharmaceutical formulation as described anywhere herein to the subject. Also provided herein are methods of treating or preventing a disease in a subject by administering a therapeutically effective amount of a pharmaceutical formulation as described anywhere herein to the subject.

In one embodiment, the subject is a human. In one embodiment, the subject is a human under 2 years of age. In one embodiment, the subject is a premature baby under 6 weeks of age.

In embodiments, the formulation is administered to a subject subcutaneously or by injection.

Suitably, the formulations are a liquid formulation or a frozen formulation.

Also provided herein are methods of preparing a pharmaceutical formulation comprising preparing a pharmaceutical formulation as described herein, and suitably loading the pharmaceutical formulation into a syringe to form a pre-filled syringe.

Suitably, the pharmaceutical formulations described herein are prepared in sterile water, or are resuspended in sterile water for injection at the desired volume.

In exemplary embodiments, the pharmaceutical formulations have a volume of about 0.1 mL to about 20.0 mL, more suitably about 0.5 mL to about 15.0 mL, about 0.5 mL to about 12.0 mL, about 1.0 mL to about 10.0 mL, about 1.0 mL to about 5.0 mL, about 1.0 mL to about 2.0 mL or about 0.5 mL, about 0.6 mL, about 0.7 mL, about 0.8 mL, about 0.9 mL, about 1.0 mL, about 1.1 mL, about 1.2 mL, about 1.3 mL, about 1.4 mL, about 1.5 mL, about 1.6 mL, about 1.7 mL, about 1.8 mL, about 1.9 mL, about 2.0 mL, about 2.1 mL, about 2.2 mL, about 2.3 mL, about 2.4 mL, about 2.5 mL, about 2.6 mL, about 2.7 mL, about 2.8 mL, about 2.9 mL, or about 3.0 mL, including any ranges or values within these ranges.

While in suitable embodiments, the pharmaceutical formulations described herein are liquid formulations, i.e., pharmaceutical formulations prepared in sterile water or water for injection (WFI), the pharmaceutical formulations can also be frozen formulations or previously lyophilized formulations.

The present invention also provides a lyophilized cake which is capable of being reconstituted using only sterile water into a formulation according to the invention as described herein. It will be understood that the ratio of antibody: ionic excipient will be the same in the lyophilized cake as in the post-lyophilized formulation. In one embodiment, the ratio of antibody: ionic excipient is in the range 450:1 to 40:1. Where the formulation has been lyophilized, the concentrations provided herein for the formulation are the post-reconstitution concentrations and thus are the concentrations in the so-called ‘drug product’. By way of example, if a half-reconstitution strategy is used (where half the volume of water removed during lyophilization is returned during reconstitution), then after reconstitution, the concentration of the antibody will be twice what it was prior to lyophilization i.e. twice what is was in the so-called pre-lyophilization ‘drug-substance’ composition. It will therefore be understood that the present invention further provides a composition capable of being lyophilized to form a lyophilized cake, wherein the lyophilized cake is capable of being reconstituted using only sterile water into a formulation according to the invention as described herein. Suitable reconstitution strategies will be known to those skilled in the art.In embodiments, it is desirable to prepare frozen formulations by providing a liquid pharmaceutical formulation as described herein, and freezing the formulation under appropriate conditions. For example, the frozen formulations can be provided by freezing the liquid formulations to less than 0 °C, more suitably to about -20 °C, about -40 °C, about -60 °C, or suitably to about -80 °C. The pharmaceutical formulations are also suitably prepared as liquid formulations and stored about 2 °C to about 8 °C, or about 2 °C, about 3 °C, about 4 °C, about 5 °C, about 6 °C, about 7 °C or about 8 °C.

Suitable protocols and methods for preparing lyophilized pharmaceutical formulations from liquid and/or frozen formulations are known in the art.

Stability of Formulations

In exemplary embodiments, the formulations described herein are stable for extended periods of storage at room temperature or at a temperature range of about 2 °C to about 8 °C, suitably about 5 °C. As used herein, room temperature is generally in the range of about 22 °C to about 25 °C. Suitably the pharmaceutical formulations are stable after storage at about 2 °C to about 8 °C (e.g. 5 °C) for at least six (6) months. As used herein, the term “stable” for a period of storage (or “stability”) is used to indicate that the formulations resist aggregation, degradation, half antibody formation, and/or fragmentation. The stability of the monoclonal antibodies can be assessed by degrees of aggregation, degradation, half antibody formation or fragmentation, as measured by high performance size exclusion chromatography (HPSEC), static light scattering (SLS), Fourier Transform Infrared Spectroscopy (FTIR), circular dichroism (CD), urea unfolding techniques, intrinsic tryptophan fluorescence, differential scanning calorimetry, and/or ANS binding techniques, compared to a reference.

The overall stability of a pharmaceutical formulation comprising monoclonal antibodies can be assessed by various immunological assays including, for example, ELISA and radioimmunoassay using isolated antigen molecules.

The phrase “low to undetectable levels of aggregation” as used herein refers to pharmaceutical formulations containing no more than about 5 %, no more than about 4 %, no more than about 3 %, no more than about 2 %, no more than about 1 %, or no more than about 0.5 % aggregation by weight of protein as measured by high performance size exclusion chromatography (HPSEC) or static light scattering (SLS) techniques. Suitably, the pharmaceutical formulations exhibit ≤ 5.0 % aggregation, more suitably ≤ 4.0 % aggregation, ≤ 3.0 % aggregation, ≤ 2.0 % aggregation, ≤ 1.0 % aggregation, or 0.5 % aggregation. Suitably, the liquid pharmaceutical formulations and/or frozen pharmaceutical formulations exhibit ≤ 5.0 % aggregation, more suitably ≤ 4.0 % aggregation, ≤ 3.0 % aggregation, ≤ 2.0 % aggregation, ≤ 1.0 % aggregation, or 0.5 % aggregation.

The term "low to undetectable levels of fragmentation" as used herein refers to pharmaceutical formulations containing equal to or more than about 80 %, about 85 %, about 90 %, about 95 %, about 98 %, or about 99 % of the total monoclonal antibody, for example, in a single peak as determined by HPSEC, or reduced Capillary Gel Electrophoresis (rCGE), representing the non-degraded monoclonal antibody, or a non-degraded fragment thereof, and containing no other single peaks having more than about 5 %, more than about 4 %, more than about 3 %, more than about 2 %, more than about 1 %, or more than about 0.5 % of the total monoclonal antibody. Fragmentation may be measured suitably in IgG4 monoclonal antibodies.

Without wishing to be bound by theory, it is thought that decreased self-aggregation is due to improved colloidal stability, as evidenced by increased kD value.

In exemplary embodiments, the formulations described herein have reduced opalescence and decreased phase separation as visual observation, light scattering, nephelometry and turbidimetric methods.

Further embodiments, features, and advantages of the embodiments, as well as the structure and operation of the various embodiments, are described in detail below with reference to accompanying drawings.

EXAMPLES

EXAMPLE 1 – IgG1 Formulation

MEDI8897 is a human IgG1κ- YTE monoclonal antibody directed against RSV-F protein. Three amino acid substitutions (M252Y/S254T/T256E; called YTE) in the CH2 region of the Fc domain were introduced to increase the serum half-life of MEDI8897.

Sequence information for MEDI8897 is provided in Figures 1 and 2. MEDI8897 pI was measured by cIEF to be 6.4-6.7 with the main peak at 6.4. The pI overlaps with the formulation buffer range (5.5-6.5) suggesting potential issues with manufacturing, formulation and storage stability.

MEDI8897 thermal stability was measured by differential scanning calorimetry. Tm1 was found to be 61°C while Tm2 was 82°C. Tm1 of 61°C meets the CDTP criteria of Tm1 > 50°C.

Stability Summary

Upon receipt of MEDI8897 in the default developability buffer (25 mM Histidine, 7% sucrose, pH 6.0), phase separation was observed at 2 to 8°C. The supernatant layer had a protein concentration of 75 mg/ml while the bottom layer was 125 mg/ml. Upon equilibration at 25°C the two distinct phases disappeared and only one single phase was observed. The phase separation at 2 to 8°C was thought to be due to the pI of MEDI8897 which is close to the formulation pH of 6.0. A scouting study was initiated to find a more appropriate formulation buffer for MEDI8897 stability assessment, targeting a condition which maintained solubility and prevented phase separation of MEDI8897 at 100 mg/ml.

Formulating in the default developability buffer (25 mM histidine, 7% sucrose) at pH's < 5.9 or > 6.7 mitigated phase separation. Addition of 75 mM NaCl to the developability buffer between pH 5.0 and 6.7 also mitigated phase separation. Finally, acetate and phosphate buffers at pH values away from the pI also mitigated phase separation. Based on these screening studies and previous knowledge of mAb's with pI's within the formulation space, an alternate developability buffer (25mM His/HisHCl, 75mM NaCl, 4% Sucrose, 0.02% PS80, pH 6.0) was selected for evaluation.

kD Studies

For the first kD screen, all samples were evaluated in 25 mM Histidine pH 5.5 base buffer from 2-10 mg/ml at 25°C. This buffer was chosen in lieu of pH 6.0 because MEDI8897 is more soluble at pH 5.5, facilitating DLS measurements which are sensitive to insoluble particles. Ionic excipients including arginine-HCl, lysine-HCl and NaCl were evaluated at 10, 25, 50, 75 and 100 mM concentrations. In addition, proline, alanine,

Na_2SO_4 and histidine were evaluated at the 100 mM concentration only. Finally, 2, 4, and 6% sucrose were evaluated to determine if sucrose influences protein-protein interactions. All conditions were compared to a buffer control (25 mM Histidine pH 5.5).

The control samples showed distinct protein-protein interactions, with the hydrodynamic radius increasing from 6.2 to 7.8 nm from 2-10 mg/ml. Arginine-HCl, lysine-HCl and NaCl showed reduction of protein-protein interactions starting at 25 mM concentrations as evidenced by no increase in hydrodynamic size over the 2-10 mg/ml concentration range. No additional effects were seen between 25 and 100 mM. At 100 mM concentration, proline and alanine showed PPI similar to the control while Na_2SO_4 and Histidine mitigated PPI. Finally, sucrose concentration showed no impact on PPI. This data illustrates that charged excipients (Arg-HCl, Lys-HCl, Histidine and Na_2SO_4) mitigate protein-protein interactions while neutral excipients (sucrose, proline, alanine) do not mitigate PPI. Therefore, addition of ionic excipients at pH 5.5 reduced phase separation at 100 mg/ml.

40°C Stability Evaluation

Based on kD screening, several conditions were selected for 40°C stability evaluation. Table 11 summarizes the formulation conditions and 1 month degradation rates seen at 40°C.

Table 11 40°C Stability Rates, Formulation Screen 1- Excipient Screening

Number	Excipient	Conc (mM)	% Mon/ mo	% Agg/mo	% Frag/mo
1	NaCl	25	-5.9	4.2	1.8
2	NaCl	75	-6.1	4.1	1.9
3	NaCl	95	-5.4	3.5	1.9
4	NaCl	120	-5.4	3.5	1.9
5	Arg-HCl	25	-5.4	3.5	1.8
6	Arg-HCl	75	-4.8	2.8	2.0
7	Arg-HCl	95	-4.5	2.6	1.9

Table 11 40°C Stability Rates, Formulation Screen 1- Excipient Screening

Number	Excipient	Conc (mM)	% Mon/ mo	% Agg/mo	% Frag/mo
8	Arg-HCl	120	-4.8	2.8	2.0
9	Lys-HCl	25	-5.7	3.9	1.9
10	Lys-HCl	75	-5.0	2.7	2.3
11	Lys-HCl	95	-5.1	3.1	2.0
12	Lys-HCl	120	-4.9	2.9	2.0

Base buffer for this study was 25 mM Histidine pH 6.0

This study illustrates that arginine and lysine are more stabilizing than NaCl. In addition, 75 mM and above appears to stabilize against aggregation. Based on this study, arginine was selected as the most stabilizing lyo-friendly excipient and was moved forward to the next set of studies.

Drug Product Stability on Final Lyo Cycle/ Representative Material

Stability was evaluated in formulation sciences to complement the IND-enabling stability studies as this was the first representative material to complete the lyophilization step. Three months of data was collected for the post reconstitution formulation of 100 mg/ml in 30 mM L-histidine/L-histidine hydrochloride monohydrate, 80 mM L-arginine hydrochloride, 120 mM sucrose, 0.04% (w/v) polysorbate 80, pH 6.0. Results are shown in Figure 3. Storage at 2-8°C showed virtually no change during the 3 month period, confirming the suitability of the formulation and lyo cycle for clinical use. These data thus demonstrate that the formulation provides appropriate stability and solubility and is suitable as a cycle 1 formulation.

Table 12 Drug Product Stability 3 Month Data Summary

Temperature	HIAC (≥10 µm)	HIAC (≥25 µm)	Bioassay	Recon Time	VI	KF
2-8°C	216	108	97%	2 min	< STD1	1.3%
25°C	522	90	97%	3 min	< STD1	1.4%
40°C	126	0	90%	3 min	< STD2	1.7%

All documents, patents, journal articles and other materials cited in the present application are hereby incorporated by reference.

Although the present invention has been fully described in conjunction with several embodiments thereof with reference to the accompanying drawings, it is to be understood that various changes and modifications can be apparent to those skilled in the art. Such changes and modifications are to be understood as included within the scope of the present invention as defined by the appended claims, unless they depart there from.

The invention may be further defined by reference to the following numbered paragraphs.

Paragraph 1. A formulation comprising:

i. An anti-RSV monoclonal antibody; and

ii. an ionic excipient;

wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater (e.g., about 50 mg/ml to about 200 mg/ml, to about 175 mg/ml, to about 165 mg/ml, to about 150 mg/l or to about 125mg/ml) and the ionic excipient is present at a a concentration of about 50 to about 150 mM and the formulation has a pH of about 5.5 to about 7.5.

Paragraph 2. A formulation according to paragraph 1, wherein the monoclonal antibody has a pI in the range of pH 6.4 to pH 7.5.

Paragraph 3. A formulation according to paragraph 1 or paragraph 2, wherein the monoclonal antibody has a pI in the range of about pH 6.4.

Paragraph 4. A formulation according to any one of the preceding paragraphs, wherein the monoclonal antibody is an IgG1 monoclonal antibody.

Paragraph 5. A formulation according to any one of the preceding paragraphs, wherein the monoclonal antibody has light chain CDR sequences:

CDR-L1 of SEQ ID NO: 3
CDR-L2 of SEQ ID NO: 4
CDR-L3 of SEQ ID NO: 5
and heavy chain CDR sequences:
CDR-H1 of SEQ ID NO: 6
CDR-H2 of SEQ ID NO: 7
CDR-H3 of SEQ ID NO: 8.

Paragraph 6. A formulation according to any one of the preceding paragraphs, wherein the monoclonal antibody has a light chain variable region sequence of SEQ ID NO: 9 and a heavy chain variable region sequence of SEQ ID NO: 10.

Paragraph 7. A formulation according to any one of the preceding paragraphs, wherein the monoclonal antibody has a light chain sequence of SEQ ID NO: 1 and a heavy chain sequence of SEQ ID NO: 2.

Paragraph 8. A formulation according to any one of the preceding paragraphs, wherein the monoclonal antibody is present in the formulation at a concentration of about 100 mg/ml to about 165 mg/ml.

Paragraph 9. A formulation according to paragraph 8, wherein the monoclonal antibody is present in the formulation at a concentration of about 100 mg/ml.

Paragraph 10. A formulation according to any one of the preceding paragraphs, wherein the formulation has a pH in the range of about pH 5.7 to about pH 6.1.

Paragraph 11. A formulation according to paragraph 10, wherein the formulation has a pH of about pH 6.0.

Paragraph 12. A formulation according to any one of the preceding paragraphs, wherein the ionic excipient is a salt.

Paragraph 13. A formulation according to paragraph 12, wherein the salt is arginine hydrochloride.

Paragraph 14. A formulation according to any one of the preceding paragraphs, wherein the ionic excipient is present at a concentration of about 75 mM to about 100 mM.

Paragraph 15. A formulation according to paragraph 14, wherein the ionic excipient is present at a concentration of about 80 mM.

Paragraph 16. A formulation according to any one of the preceding paragraphs, wherein the formulation further comprises a sugar.

Paragraph 17. A formulation according to paragraph 16, wherein the sugar is sucrose.

Paragraph 18. A formulation according to any one of paragraphs 16 to 17, wherein the sugar is present at a concentration of about 100 mM to about 140 mM.

Paragraph 19. A formulation according to paragraph 18, wherein the sugar is present at a concentration of about 120 mM.

Paragraph 20. A formulation according to any one of the preceding paragraphs, wherein the formulation further comprises one or more buffers.

Paragraph 21. A formulation according to paragraph 20, wherein the one or more buffers is selected from histidine, histidine hydrochloride, and histidine/ histidine hydrochloride.

Paragraph 22. A formulation according to paragraph 21, wherein the one or more buffers is L-histidine/ L-histidine hydrochloride monohydrate.

A formulation according to any one of paragraphs 20 to 23, wherein the one or more buffers is present at a concentration of about 10 mM to about 50 mM.

Paragraph 23. A formulation according to paragraph 23, wherein the one or more buffers is present at a concentration of about 30 mM.

Paragraph 24. A formulation according to any one of the preceding paragraphs, wherein the formulation further comprises a surfactant.

Paragraph 25. A formulation according to paragraph 25, wherein the surfactant is a polysorbate.

Paragraph 26. A formulation according to paragraph 26, wherein the surfactant is polysorbate-80.

Paragraph 27. A formulation according to any one of paragraphs 25 to 27, wherein the surfactant is present in the formulation at a concentration from about 0.001 % (w/v) to about 0.07 % (w/v).

Paragraph 28. A formulation according to paragraph 28, wherein the surfactant is present in the formulation at a concentration of about 0.02% (w/v).

Paragraph 29. A formulation according to any one of the preceding paragraphs, wherein the formulation further comprises one or more additional excipients, including for example, one or more sugars, salts, amino acids, polyols, chelating agents, emulsifiers and/or preservatives.

Paragraph 30. A formulation according to any one of paragraphs 1 to 29, which is a pharmaceutical formulation.

Paragraph 31. A pharmaceutical formulation according to paragraph 30 for use as a medicament.

Paragraph 32. A pharmaceutical formulation according to paragraph 31 for use in the treatment of a disease.

Paragraph 33. A method of treating or preventing a disease in a subject comprising administering a pharmaceutical formulation according to paragraph 31 to the subject.

Paragraph 34. An isolated monoclonal antibody having light chain CDR sequences:

CDR-L1 of SEQ ID NO: 3

CDR-L2 of SEQ ID NO: 4

CDR-L3 of SEQ ID NO: 5

and heavy chain CDR sequences:

CDR-H1 of SEQ ID NO: 6

CDR-H2 of SEQ ID NO: 7

CDR-H3 of SEQ ID NO: 8.

Paragraph 35. An isolated monoclonal antibody according to paragraph 35, wherein the monoclonal antibody has a light chain variable region sequence of SEQ ID NO: 9 and a heavy chain variable region sequence of SEQ ID NO: 10.

Paragraph 36. An isolated monoclonal antibody according to paragraph 35 or paragraph 36, wherein the monoclonal antibody has a light chain sequence of SEQ ID NO: 1 and a heavy chain sequence of SEQ ID NO: 2.

Paragraph 37. An isolated monoclonal antibody according to any one of paragraphs 35 to 37, wherein the antibody is an IgG1 antibody.

Paragraph 38. A pharmaceutical composition comprising an isolated antibody as defined in any one of paragraphs 35 to 38.

Paragraph 39. An isolated monoclonal antibody according to any one of paragraphs 35 to 38 or a pharmaceutical composition according to paragraph 39 for use as a medicament.

Paragraph 40. An isolated monoclonal antibody according to any one of paragraphs 35 to 38 or a pharmaceutical composition according to paragraph 39 for use in the treatment of a disease.

Paragraph 41. A method of treating or preventing a disease in a subject comprising administering an isolated monoclonal antibody according to any one of paragraphs 35 to 38 or a pharmaceutical composition according to paragraph 39 to the subject.

Paragraph 42. A lyophilized cake capable of being reconstituted using only sterile water into a formulation as defined in any one of paragraphs 1 to 31.

Paragraph 43. A composition capable of being lyophilized to form a lyophilized cake, wherein the lyophilized cake is capable of being reconstituted using only sterile water into a formulation as defined in any one of paragraphs 1 to 31.

WHAT IS CLAIMED IS:

1. A formulation comprising:
    i. an anti-RSV monoclonal antibody; and
    ii. an ionic excipient;

   wherein the monoclonal antibody is present at a concentration of about 50mg/ml or greater and the ionic excipient is present at a concentration of about 50 to about 150 mM and the formulation has a pH of about 5.5 to about 7.5.

2. A formulation according to claim 1, wherein the monoclonal antibody has a pI in the range of pH 6.4 to pH 7.5.

3. A formulation according to claim 1 or claim 2, wherein the monoclonal antibody has a pI in the range of about pH 6.4.

4. A formulation according to any one of the preceding claims, wherein the monoclonal antibody is an IgG1 monoclonal antibody.

5. A formulation according to any one of the preceding claims, wherein the monoclonal antibody has light chain CDR sequences:
   CDR-L1 of SEQ ID NO: 3
   CDR-L2 of SEQ ID NO: 4
   CDR-L3 of SEQ ID NO: 5
   and heavy chain CDR sequences:
   CDR-H1 of SEQ ID NO: 6
   CDR-H2 of SEQ ID NO: 7
   CDR-H3 of SEQ ID NO: 8.

6. A formulation according to any one of the preceding claims, wherein the monoclonal antibody has a light chain variable region sequence of SEQ ID NO: 9 and a heavy chain variable region sequence of SEQ ID NO: 10.

7. A formulation according to any one of the preceding claims, wherein the monoclonal antibody has a light chain sequence of SEQ ID NO: 1 and a heavy chain sequence of SEQ ID NO: 2.

8. A formulation according to any one of the preceding claims, wherein the monoclonal antibody is present in the formulation at a concentration of about 100 mg/ml to about 165 mg/ml.

9. A formulation according to claim 8, wherein the monoclonal antibody is present in the formulation at a concentration of about 100 mg/ml.

10. A formulation according to any one of the preceding claims, wherein the formulation has a pH in the range of about pH 5.7 to about pH 6.1.

11. A formulation according to claim 10, wherein the formulation has a pH of about pH 6.0.

12. A formulation according to any one of the preceding claims, wherein the ionic excipient is a salt.

13. A formulation according to claim 12, wherein the salt is arginine hydrochloride.

14. A formulation according to any one of the preceding claims, wherein the ionic excipient is present at a concentration of about 75 mM to about 100 mM.

15. A formulation according to claim 14, wherein the ionic excipient is present at a concentration of about 80 mM.

16. A formulation according to any one of the preceding claims, wherein the formulation further comprises a sugar.

17. A formulation according to claim 16, wherein the sugar is sucrose.

18. A formulation according to any one of claims 16 to 17, wherein the sugar is present at a concentration of about 100 mM to about 140 mM.

19. A formulation according to claim 18, wherein the sugar is present at a concentration of about 120 mM.

20. A formulation according to any one of the preceding claims, wherein the formulation further comprises one or more buffers.

21. A formulation according to claim 20, wherein the one or more buffers is selected from histidine, histidine hydrochloride, and histidine/ histidine hydrochloride.

22. A formulation according to claim 21, wherein the one or more buffers is L-histidine/ L-histidine hydrochloride monohydrate.

23. A formulation according to any one of claims 20 to 22, wherein the one or more buffers is present at a concentration of about 10 mM to about 50 mM.

24. A formulation according to claim 23, wherein the one or more buffers is present at a concentration of about 30 mM.

25. A formulation according to any one of the preceding claims, wherein the formulation further comprises a surfactant.

26. A formulation according to claim 25, wherein the surfactant is a polysorbate.

27. A formulation according to claim 26, wherein the surfactant is polysorbate-80.

28. A formulation according to any one of claims 25 to 27, wherein the surfactant is present in the formulation at a concentration from about 0.001 % (w/v) to about 0.07 % (w/v).

29. A formulation according to claim 28, wherein the surfactant is present in the formulation at a concentration of about 0.02% (w/v).

30. A formulation according to any one of the preceding claims, wherein the formulation further comprises one or more additional excipients, including for example, one or more sugars, salts, amino acids, polyols, chelating agents, emulsifiers and/or preservatives.

31. A formulation according to any one of claims 1 to 30, which is a pharmaceutical formulation.

32. A pharmaceutical formulation according to claim 31 for use as a medicament.

33. A pharmaceutical formulation according to claim 31 for use in the treatment of a disease.

34. A method of treating or preventing a disease in a subject comprising administering a pharmaceutical formulation according to claim 31 to the subject.

35. A lyophilized cake capable of being reconstituted using only sterile water into a formulation as defined in any one of claims 1 to 31.

36. A composition capable of being lyophilized to form a lyophilized cake, wherein the lyophilized cake is capable of being reconstituted using only sterile water into a formulation as defined in any one of claims 1 to 31.

MEDI8897 HEAVY CHAIN NUCLEOTIDE SEQUENCES AND TRANSLATION

```
       Q   V   Q   L   V   Q   S   G   A   E   V   K   K   P   G   S   S   V   M   V
   1  CAA GTG CAG CTG GTG CAG TCT GGC GCC GAA GTG AAG AAA CCC GGC TCC TCC GTG ATG GTG

       S   C   Q   A   S   G   G   L   L   E   D   Y   I   I   N   W   V   R   Q   A
  61  TCC TGC CAG GCT TCT GGC GGC CTG CTG GAA GAT TAC ATC ATC AAC TGG GTG CGA CAG GCC

       P   G   Q   G   P   E   W   M   G   G   I   I   P   V   L   G   T   V   H   Y
 121  CCA GGC CAG GGA CCT GAA TGG ATG GGC GGA ATC ATC CCC GTG CTG GGC ACC GTG CAC TAC

       G   P   K   F   Q   G   R   V   T   I   T   A   D   E   S   T   D   T   A   Y
 181  GGC CCT AAG TTC CAG GGC AGA GTG ACC ATC ACC GCC GAC GAG TCT ACC GAC ACC GCC TAC

       M   E   L   S   S   L   R   S   E   D   T   A   M   Y   Y   C   A   T   E   T
 241  ATG GAA CTG TCC TCC CTG CGG AGC GAG GAC ACC GCC ATG TAC TAC TGC GCC ACC GAG ACA

       A   L   V   V   S   E   T   Y   L   P   H   Y   F   D   N   W   G   Q   G   T
 301  GCC CTG GTG GTG TCC GAG ACA TAC CTG CCC CAC TAC TTC GAC AAC TGG GGC CAG GGA ACC

       L   V   T   V   S   S | A   S   T   K   G   P   S   V   F   P   L   A   P   S
 361  CTC GTG ACC GTC TCC TCA|GCC TCC ACC AAG GGC CCA TCG GTC TTC CCC CTG GCA CCC TCC

       S   K   S   T   S   G   G   T   A   A   L   G   C   L   V   K   D   Y   F   P
 421  TCC AAG TCC ACC TCC GGC GGC ACC GCC GCT CTG GGC TGC CTG GTG AAG GAC TAC TTC CCT

       E   P   V   T   V   S   W   N   S   G   A   L   T   S   G   V   H   T   F   P
 481  GAG CCT GTG ACC GTG TCC TGG AAC TCT GGC GCC CTG ACC TCT GGC GTG CAC ACC TTC CCT

       A   V   L   Q   S   S   G   L   Y   S   L   S   S   V   V   T   V   P   S   S
 541  GCC GTG CTG CAG TCC TCC GGC CTG TAC TCC CTG TCC TCC GTG GTG ACA GTG CCT TCC TCC

       S   L   G   T   Q   T   Y   I   C   N   V   N   H   K   P   S   N   T   K   V
 601  TCC CTG GGC ACC CAG ACC TAC ATC TGC AAC GTG AAC CAC AAG CCC AGC AAC ACC AAG GTG

       D   K   R   V   E   P   K   S   C   D   K   T   H   T   C   P   P   C   P   A
 661  GAC AAG AGA GTT GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC CCA CCG TGC CCA GCA

       P   E   L   L   G   G   P   S   V   F   L   F   P   P   K   P   K   D   T   L
 721  CCT GAA CTC CTG GGG GGA CCG TCA GTC TTT CTG TTC CCT CCT AAG CCT AAG GAC ACC CTG

       Y   I   T   R   E   P   E   V   T   C   V   V   V   D   V   S   H   E   D   P
 781  TAC ATC ACC CGG GAG CCT GAA GTG ACC TGC GTG GTG GTG GAT GTG TCC CAC GAG GAC CCT

       E   V   K   F   N   W   Y   V   D   G   V   E   V   H   N   A   K   T   K   P
 841  GAG GTG AAG TTC AAT TGG TAC GTG GAC GGC GTG GAG GTG CAC AAC GCC AAG ACC AAG CCT

       R   E   E   Q   Y   N   S   T   Y   R   V   V   S   V   L   T   V   L   H   Q
 901  CGG GAG GAG CAG TAC AAC TCC ACC TAC CGG GTG GTG TCT GTG CTG ACC GTG CTG CAC CAG

       D   W   L   N   G   K   E   Y   K   C   K   V   S   N   K   A   L   P   A   P
 961  GAC TGG CTG AAC GGC AAA GAA TAC AAG TGC AAA GTC TCC AAC AAG GCC CTG CCT GCC CCC

       I   E   K   T   I   S   K   A   K   G   Q   P   R   E   P   Q   V   Y   T   L
1021  ATC GAG AAA ACC ATC TCC AAA GCC AAA GGG CAG CCC CGA GAA CCA CAG GTG TAC ACC CTG

       P   P   S   R   E   E   M   T   K   N   Q   V   S   L   T   C   L   V   K   G
1081  CCT CCC TCC CGC GAG GAG ATG ACC AAG AAC CAG GTG TCC CTG ACC TGT CTG GTG AAG GGC

       F   Y   P   S   D   I   A   V   E   W   E   S   N   G   Q   P   E   N   N   Y
1141  TTC TAC CCT TCC GAT ATC GCC GTG GAG TGG GAG TCC AAC GGC CAG CCT GAG AAC AAC TAC

       K   T   T   P   P   V   L   D   S   D   G   S   F   F   L   Y   S   K   L   T
1201  AAG ACC ACC CCT CCT GTG CTG GAC TCC GAC GGC TCC TTC TTC CTG TAC TCC AAG CTG ACC

       V   D   K   S   R   W   Q   Q   G   N   V   F   S   C   S   V   M   H   E   A
1261  GTG GAC AAG TCC CGG TGG CAG CAG GGC AAC GTG TTC TCC TGC TCC GTG ATG CAC GAG GCT

       L   H   N   H   Y   T   Q   K   S   L   S   L   S   P   G   K
1321  CTG CAC AAC CAC TAC ACC CAG AAA AGC CTC TCC CTG TCT CCG GGT AAA
```

(CDRs ARE UNDERLINED, AMINO ACID DIFFERENCES FROM ALLELIC CONSTANT REGIONS HAVE BEEN CIRCLED AND DIVISION BETWEEN THE VARIABLE AND CONSTANT REGIONS MARKED BY A '|')

Fig. 1

MEDI8897 LIGHT CHAIN NUCLEOTIDE SEQUENCES AND TRANSLATION

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     D   I   Q   M   T   Q   S   P   S   S   L   S   A   A   V   G   D   R   V   T
  1  GAC ATC CAG ATG ACC CAG TCC CCC TCC TCT CTG TCT GCT GCC GTG GGC GAC AGA GTG ACC

     I   T   C   Q   A   S   Q   D   I   V   N   Y   L   N   W   Y   Q   Q   K   P
 61  ATC ACC TGT CAG GCC TCC CAG GAC ATC GTG AAC TAC CTG AAC TGG TAT CAG CAG AAG CCC

     G   K   A   P   K   L   L   I   Y   V   A   S   N   L   E   T   G   V   P   S
121  GGC AAG GCC CCC AAG CTG CTG ATC TAC GTG GCC TCC AAC CTG GAA ACC GGC GTG CCC TCC

     R   F   S   G   S   G   S   G   T   D   F   S   L   T   I   S   S   L   Q   P
181  AGA TTC TCC GGC TCT GGC TCT GGC ACC GAC TTC AGC CTG ACC ATC TCC AGC CTG CAG CCT

     E   D   V   A   T   Y   Y   C   Q   Q   Y   D   N   L   P   L   T   F   G   G
241  GAG GAC GTG GCC ACC TAC TAC TGC CAG CAG TAC GAC AAC CTG CCC CTG ACC TTT GGC GGA

     G   T   K   V   E   I   K  |R   T   V   A   A   P   S   V   F   I   F   P   P
301  GGC ACC AAG GTG GAG ATC AAA|CGA ACT GTG GCT GCA CCA TCT GTC TTC ATC TTC CCC CCC

     S   D   E   Q   L   K   S   G   T   A   S   V   V   C   L   L   N   N   F   Y
361  AGC GAC GAG CAG CTG AAG AGC GGC ACC GCC TCC GTG GTG TGC CTG CTG AAC AAC TTC TAC

     P   R   E   A   K   V   Q   W   K   V   D   N   A   L   Q   S   G   N   S   Q
421  CCC CGC GAG GCC AAG GTG CAG TGG AAG GTG GAC AAC GCC CTG CAG TCC GGC AAC AGC CAG

     E   S   V   T   E   Q   D   S   K   D   S   T   Y   S   L   S   S   T   L   T
481  GAG AGC GTC ACC GAG CAG GAC AGC AAG GAC TCC ACC TAC AGC CTG AGC AGC ACC CTG ACC

     L   S   K   A   D   Y   E   K   H   K   V   Y   A   C   E   V   T   H   Q   G
541  CTG AGC AAG GCC GAC TAC GAG AAG CAC AAG GTG TAC GCC TGC GAG GTG ACC CAC CAG GGC

     L   S   S   P   V   T   K   S   F   N   R   G   E   C
601  CTG TCC AGC CCC GTG ACC AAG AGC TTC AAC AGG GGC GAG TGC
```

Fig. 2

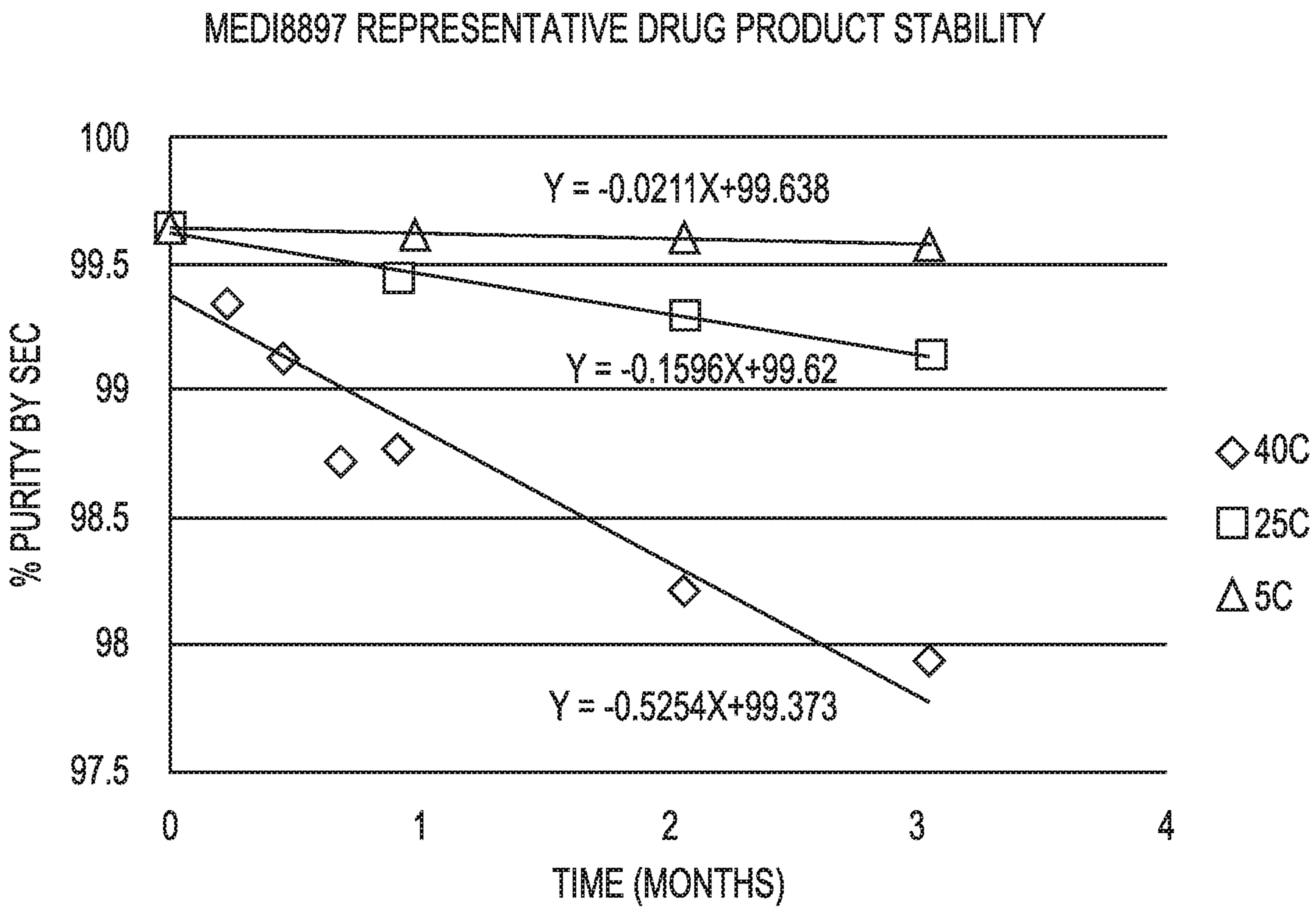
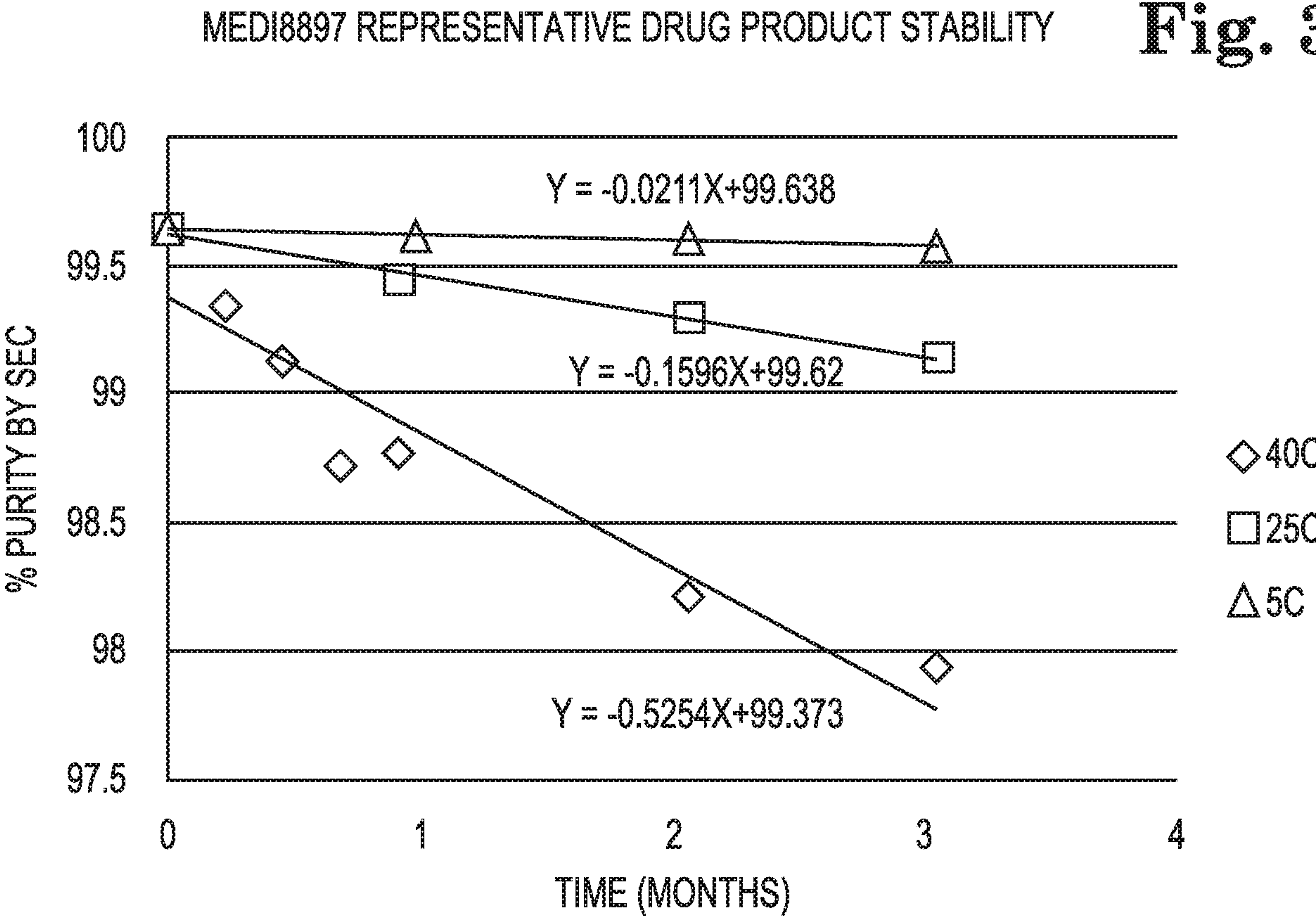

MEDI8897 REPRESENTATIVE DRUG PRODUCT STABILITY
100
99.5
99
98.5
98
97.5
% PURITY BY SEC
Y = -0.0211X+99.638
Y = -0.1596X+99.62
Y = -0.5254X+99.373
0
1
2
3
4
TIME (MONTHS)
40C
25C
5C

Fig. 3

Fig. 3


MEDI8897 REPRESENTATIVE DRUG PRODUCT STABILITY
100
99.5
99
98.5
98
97.5
% PURITY BY SEC
Y = -0.0211X+99.638
Y = -0.1596X+99.62
Y = -0.5254X+99.373
0
1
2
3
4
TIME (MONTHS)
40C
25C
5C