

comprehensive structural and functional assessment of the molecule is typically required to identify such attributes and understand their impact on the properties of the molecule. An understanding of a molecule's attributes is important to ensure production of a consistent product.

[0006] Variants of the biologic can arise during the manufacturing process or under storage conditions. Such product variants can be categorized as product-related substances or product-related impurities. Product-related substances are those molecular variants of the desired product formed during manufacture or storage of the product which have properties comparable to those of the desired product, and are not considered impurities. Conversely, product-related impurities are molecular variants of the desired product, which do not have properties comparable to those of the desired product with respect to product efficacy and patient safety. Thus, identification and characterization of product-related impurities in particular is useful for the manufacture and quality control of the biologic drug product.

SUMMARY

[0007] The present disclosure is based, in part, on the identification and characterization of product-related impurities of erenumab, particularly variants of erenumab that have reduced functional activity. Control and monitoring of the amounts of these variants in therapeutic erenumab compositions ensures that the erenumab compositions have the requisite potency to produce the desired clinical effects. In one aspect, the present disclosure refers to a composition comprising: (i) erenumab, wherein erenumab comprises two heavy chains and two light chains, each said heavy chain having a sequence of SEQ ID NO: 1 or SEQ ID NO: 3 and each said light chain having a sequence of SEQ ID NO: 2 or SEQ ID NO: 4; (ii) ~~and one or more erenumab variants, wherein the one or more erenumab variants comprises an erenumab isomerization variant, wherein the isomerization variant has an isoaspartic acid residue or a succinimide at amino acid position 105 in either or both heavy chains of erenumab;~~ and (iii) an erenumab deamidation variant, wherein the deamidation variant has an aspartic acid residue, a succinimide, or an isoaspartic acid residue at amino acid position 102 in either or both heavy chains of erenumab, and wherein the amount of the isomerization variant and deamidation variant in the composition is ~~less than about from 1% to 30~~15%. Accordingly, in some examples, the present disclosure provides an erenumab composition comprising erenumab and one or more erenumab variants, wherein the erenumab variants comprise isomerization variants, deamidation variants, acidic variants, disulfide isoform variants, high molecular weight (HMW) species, or combinations thereof, wherein the amounts of the erenumab variants in the composition are controlled to within specific ranges.

[0008] In certain examples, the disclosure provides compositions comprising erenumab and one or more erenumab variants, wherein the one or more erenumab variants comprises an isomerization variant and a deamidation variant. In some examples, the isomerization variant

has an isoaspartic acid residue or succinimide at amino acid position 105 in either or both heavy chains (SEQ ID NO: 1 or SEQ ID NO: 3) of erenumab. In these and other examples, the deamidation variant has the asparagine residue at amino acid position 102 in either or both heavy chains (SEQ ID NO: 1 or SEQ ID NO: 3) of erenumab converted to an aspartic acid residue, a succinimide, or an isoaspartic acid residue. The amount of the isomerization variant and deamidation variant in the composition can be less than about 30%, less than about 15%, less than about 8%, or less than about 4%, for example, as determined by hydrophobic interaction chromatography high performance liquid chromatography (HIC-HPLC).

[0009] The disclosure also provides compositions of erenumab and one or more acidic variants of erenumab. ~~In another aspect, the present disclosure refers to a composition comprising erenumab and one or more erenumab acidic variants, wherein the amount of acidic variants in the composition is less than about 40%.~~ The amount of acidic variants in the composition can be less than about 40%, for example, from about 25% to about 38% or from about 26% to about 34%. In some examples, the amount of acidic variants in the erenumab compositions is determined by cation exchange high performance liquid chromatography (CEX-HPLC). Acidic variants of erenumab include disulfide isoform variants, deamidation variants, fragmentation variants, non-consensus glycosylation variants, HMW species, and combinations thereof. In certain examples, the acidic variants comprise disulfide isoform variants, fragmentation variants, or combinations thereof.

[0010] ~~In another aspect, the present disclosure refers to a composition comprising erenumab and one or more disulfide isoform variants thereof, wherein the one or more disulfide isoform variants comprise an IgG2-B isoform, and wherein the amount of the IgG2-B isoform in the composition is less than about 20%.~~ In some examples, the present disclosure provides compositions of erenumab and disulfide isoform variants of erenumab. The disulfide isoform variants of erenumab can comprise an IgG2-B isoform and/or an IgG2-A/B isoform. The amount of the IgG2-B isoform in the composition can be less than about 20%, for example, less than about 10%, or less than about 8%, such as from about 4% to about 6%. The amount of the IgG2-A/B isoform in the composition can be from about 20% to about 40%, from about 26% to about 38%, or from about 34% to about 37%. In certain examples, the amount of the disulfide isoforms is determined by non-reduced reversed phase high performance liquid chromatography (RP-HPLC).

[0011] The disclosure also includes compositions comprising erenumab and one or more size variants of erenumab, such as low molecular weight (LMW) species, middle molecular weight (MMW) species, and high molecular weight (HMW) species. ~~In another aspect, the present disclosure refers to a composition comprising erenumab and a high molecular weight (HMW) species of erenumab, wherein the amount of the HMW species in the composition is less than about 2.5%. In yet another aspect, the present disclosure refers to a composition comprising erenumab and one or more erenumab variants, wherein the erenumab variants comprise isomerization variants, deamidation variants, acidic variants, HMW species, or combinations thereof, wherein the composition has one or more of the following characteristics: (a) the amount of acidic variants in the composition is from about 25% to about 38% as measured by CEX-HPLC; (b) the amount of HMW species in the composition is about 2.1% or less as measured by SE-UHPLC; and (c) the amount of isomerization variants and deamidation variants in the composition is about 8% or less as measured by the pre-peaks in HIC-HPLC.~~ In certain examples, the amount of HMW species in the composition is less than about 3.0%, for example, about 2.5% or less, about 2.1% or less, about 1.8% or less, about 1.4% or less, or about 1.2% or less. In one particular example, the HMW species of erenumab is comprised predominantly of a covalently-linked dimer of erenumab. The amount of HMW species in the erenumab compositions can be determined by size exclusion ultra-high performance liquid chromatography (SE-UHPLC).

[0012] In another aspect, the present disclosure refers to a pharmaceutical formulation comprising the composition as disclosed herein and one or more pharmaceutically acceptable excipients. In yet another aspect, the present disclosure refers to a pre-filled syringe or autoinjector comprising the pharmaceutical formulation as disclosed herein. In some examples, the present disclosure also provides methods of evaluating or assessing the quality of erenumab compositions. In one example, the methods comprise obtaining an erenumab composition that contains erenumab and one or more erenumab variants; measuring the amount of one or more erenumab variants in the composition; comparing the measured amount of the one or more erenumab variants to a pre-determined reference criterion; and preparing a pharmaceutical formulation or pharmaceutical product of the erenumab composition if the comparison indicates that the pre-determined reference criterion is met. The methods may comprise one, two, or three of the following: (1) measuring the amount of isomerization variants and deamidation variants in the composition (e.g. by peak area percentage of the pre-peaks in HIC-HPLC), (2) measuring the amount of acidic variants in the composition (e.g. by peak area percentage of the acidic peaks in CEX-HPLC), and/or (3) measuring the amount of HMW species in the composition (e.g. by peak area percentage of the pre-peaks in SE-UHPLC). In certain examples, all three measurements are performed on an erenumab composition. In yet another aspect, the present disclosure refers to a method for

~~preparing a pharmaceutical formulation comprising assessing the quality of~~ an erenumab composition, ~~the method~~ comprising: (i) obtaining ~~a partially purified composition comprising an erenumab composition that contains~~ erenumab and ~~one or more~~ erenumab ~~isomerization and deamidation~~ variants, wherein erenumab comprises two heavy chains and two light chains, each said heavy chain having a sequence of SEQ ID NO: 1 or SEQ ID NO: 3 and each said light chain having a sequence of SEQ ID NO: 2 or SEQ ID NO: 4; (ii) measuring the amount of ~~one or more erenumab~~ the isomerization and deamidation variants in the ~~partially purified~~ composition using HIC-HPLC, wherein the ~~isomerization variant has an isoaspartic acid residue or a succinimide at amino acid position 105 in either or both heavy chains of erenumab and the deamidation variant has an aspartic acid residue, a succinimide, or an isoaspartic acid residue at amino acid position 102 in either or both heavy chains of erenumab~~erenumab variants ~~comprise isomerization variants, deamidation variants, acidic variants, HMW species, or combinations thereof;~~ (iii) comparing the measured amount of the ~~one or more~~ erenumab ~~isomerization and deamidation~~ variants to a pre-determined reference criterion, wherein the pre-determined reference criterion is a range from 1% to 10%; and (iv) ~~combining the erenumab composition with one or more excipients to preparing~~ prepare a the pharmaceutical formulation ~~or pharmaceutical product of the erenumab composition~~ if the comparison indicates that the pre-determined reference criterion is met.

[0013] Pharmaceutical formulations comprising the erenumab compositions described herein are also included in the disclosure. In some examples, the pharmaceutical formulations comprise an erenumab composition described herein and one or more pharmaceutically acceptable excipients, such as buffers, sugars, and surfactants. The pharmaceutical formulations can be incorporated into an injection device, such as a pre-filled syringe or autoinjector. In such examples, the injection volume for the pre-filled syringes or autoinjectors is less than about 2 mL, for example, about 1 mL.

[0014] In another aspect, the present disclosure refers to an erenumab composition ~~of any one of claims 1 to 30~~as disclosed herein for use in therapy. In yet another aspect, the present disclosure refers to a use of an erenumab composition as disclosed herein in the preparation of a medicament for treating, preventing, or reducing the occurrence of headache in a patient in need thereof. The present disclosure also includes methods of treating, preventing, or reducing the occurrence of headache in a patient in need thereof using the erenumab compositions and pharmaceutical formulations of the disclosure. In one example, the methods comprise administering to the patient a pharmaceutical formulation comprising an erenumab composition described herein. The headache can be a migraine headache, cluster headache, or other type of headache disorder, such as tension-type headache, hemiplegic migraine, menstrual migraine, and retinal migraine. In certain examples, the patient to be treated according to the methods or uses of the disclosure has or is diagnosed with migraine, such as episodic migraine or chronic migraine.

CLAIMS

What is claimed:

1. A composition comprising:

(i) erenumab, wherein erenumab comprises two heavy chains and two light chains, each said heavy chain having a sequence of SEQ ID NO: 1 or SEQ ID NO: 3 and each said light chain having a sequence of SEQ ID NO: 2 or SEQ ID NO: 4;

(ii) and one or more erenumab variants, wherein the one or more erenumab variants comprises an erenumab isomerization variant, wherein the isomerization variant has an isoaspartic acid residue or a succinimide at amino acid position 105 in either or both heavy chains of erenumab; and

(iii) an erenumab deamidation variant, wherein the deamidation variant has an aspartic acid residue, a succinimide, or an isoaspartic acid residue at amino acid position 102 in either or both heavy chains of erenumab, and

wherein the amount of the isomerization variant and deamidation variant in the composition is ~~less than about 30%~~from 1% to 15%.

~~2. The composition of claim 1, wherein the amount of the isomerization variant and deamidation variant in the composition is less than about 15%.~~

~~3. The composition of claim 1, wherein the amount of the isomerization variant and deamidation variant in the composition is less than about 8%.~~

~~4. The composition of claim 1, wherein the amount of the isomerization variant and deamidation variant in the composition is less than about 4%.~~

~~52.~~ The composition of claim 1, wherein the amount of the isomerization variant and deamidation variant in the composition is from ~~about 1%~~ to ~~about 10%~~.

~~63.~~ The composition of claim 1, wherein the amount of the isomerization variant and deamidation variant in the composition is from ~~about 1%~~ to ~~about 4%~~.

~~7. — The composition of any one of claims 1 to 6, wherein the isomerization variant has an isoaspartic acid residue or a succinimide at amino acid position 105 in either or both heavy chains (SEQ ID NO: 1 or SEQ ID NO: 3) of erenumab.~~

~~8. — The composition of any one of claims 1 to 7, wherein the deamidation variant has the asparagine residue at amino acid position 102 in either or both heavy chains (SEQ ID NO: 1 or SEQ ID NO: 3) of erenumab converted to an aspartic acid residue, a succinimide, or an isoaspartic acid residue.~~

94. The composition of any one of claims 1 to ~~83~~, wherein the amount of the isomerization variant and deamidation variant in the composition is determined by hydrophobic interaction chromatography high performance liquid chromatography (HIC-HPLC).

~~10. — A composition comprising erenumab and one or more erenumab acidic variants, wherein the amount of acidic variants in the composition is less than about 40%.~~

~~11. — The composition of claim 10, wherein the amount of acidic variants in the composition is less than about 35%.~~

~~12. — The composition of claim 10, wherein the amount of acidic variants in the composition is from about 25% to about 38%.~~

~~13. — The composition of claim 10, wherein the amount of acidic variants in the composition is from about 26% to about 34%.~~

~~14. — The composition of any one of claims 10 to 13, wherein one or more acidic variants comprise disulfide isoform variants, fragmentation variants, or combinations thereof.~~

15. — The composition of any one of claims 10 to 14, wherein the amount of acidic variants in the composition is determined by cation-exchange high performance liquid chromatography (CEX HPLC).

~~16. — A composition comprising erenumab and one or more disulfide isoform variants thereof, wherein the one or more disulfide isoform variants comprise an IgG2-B isoform, and wherein the amount of the IgG2-B isoform in the composition is less than about 20%.~~

~~17. — The composition of claim 16, wherein the amount of the IgG2-B isoform in the composition is less than about 10%.~~

~~18. — The composition of claim 16, wherein the amount of the IgG2-B isoform in the composition is from about 4% to about 6%.~~

~~19. — The composition of any one of claims 16 to 18, wherein the one or more disulfide isoform variants further comprise an IgG2-A/B isoform.~~

~~20. — The composition of claim 19, wherein the amount of the IgG2-A/B isoform in the composition is from about 34% to about 37%.~~

~~21. — The composition of any one of claims 16 to 20, wherein the amount of disulfide isoform variants in the composition is determined by non-reduced reversed phase high performance liquid chromatography (RP-HPLC).~~

~~22. — A composition comprising erenumab and a high molecular weight (HMW) species of erenumab, wherein the amount of the HMW species in the composition is less than about 2.5%.~~

~~23. — The composition of claim 22, wherein the amount of the HMW species in the composition is about 1.8% or less.~~

~~24. — The composition of claim 22, wherein the amount of the HMW species in the composition is about 1.2% or less.~~

~~25. — The composition of any one of claims 22 to 24, wherein the HMW species comprises a covalently linked dimer of erenumab.~~

~~26. The composition of any one of claims 22 to 25, wherein the amount of the HMW species in the composition is determined by size exclusion ultra high performance liquid~~

~~chromatography (SE UHPLC).27. A composition comprising erenumab and one or more erenumab variants, wherein the erenumab variants comprise isomerization variants, deamidation variants, acidic variants, HMW species, or combinations thereof, wherein the composition has one or more of the following characteristics:~~

~~—— (a) the amount of acidic variants in the composition is from about 25% to about 38% as measured by CEX HPLC;~~

~~—— (b) the amount of HMW species in the composition is about 2.1% or less as measured by SE UHPLC; and~~

~~—— (c) the amount of isomerization variants and deamidation variants in the composition is about 8% or less as measured by the pre peaks in HIC HPLC.~~

~~28. The composition of claim 27, wherein the composition has one or more of the following characteristics:~~

~~(a) the amount of acidic variants in the composition is from about 26.5% to about 33.6% as measured by CEX HPLC;~~

~~—— (b) the amount of HMW species in the composition is about 1.2% or less as measured by SE UHPLC; and~~

~~—— (c) the amount of isomerization variants and deamidation variants in the composition is about 3.2% or less as measured by the pre peaks in HIC HPLC.~~

~~295. The composition of any one of claims 1 to 284, wherein each heavy chain of erenumab ~~comprises a heavy chain~~has the sequence of SEQ ID NO: 1 and ~~each a~~ light chain of erenumab has the sequence of SEQ ID NO: 2.~~

~~306. The composition of any one of claims 1 to 284, wherein each heavy chain of erenumab ~~comprises a heavy chain~~has the sequence of SEQ ID NO: 3 and ~~a each~~ light chain of erenumab has the sequence of SEQ ID NO: 4.~~

7. The composition of claim 1, wherein each heavy chain of erenumab has the sequence of SEQ ID NO: 3 and each light chain of erenumab has the sequence of SEQ ID NO: 4, and wherein the amount of erenumab in the composition is 90% or greater as measured by the main peak in HIC-HPLC and the amount of the isomerization variant and deamidation variant in the composition is from 1% to 10% as measured by the pre-peaks in HIC-HPLC.

~~318.~~ A pharmaceutical formulation comprising the composition of any one of claims 1 to ~~30-7~~ and one or more pharmaceutically acceptable excipients.

9. The pharmaceutical formulation of claim 8, wherein the formulation comprises about 70 mg/mL of the erenumab composition, about 25 mM acetate, about 7.3% (w/v) sucrose, and about 0.010% (w/v) polysorbate 80, wherein the formulation has a pH of 5.2 ± 0.2 .

10. The pharmaceutical formulation of claim 8, wherein the formulation comprises about 140 mg/mL of the erenumab composition, about 34 mM acetate, about 6.5% (w/v) sucrose, and about 0.010% (w/v) polysorbate 80, wherein the formulation has a pH of 5.2 ± 0.2 .

11. A pre-filled syringe or autoinjector comprising the pharmaceutical formulation of claim 9 or 10.

12. The pre-filled syringe or autoinjector of claim 11, wherein the injection volume of the syringe or autoinjector is 1 mL.

~~3213.~~ An erenumab composition of any one of claims 1 to ~~30-7~~ for use in therapy.

~~3314.~~ Use of an erenumab composition of any one of claims 1 to ~~30-7~~ in the preparation of a medicament for treating, preventing, or reducing the occurrence of headache in a patient in need thereof.

~~3415.~~ The use of claim ~~3314~~, wherein the headache is migraine.

~~3516.~~ The use of claim ~~3415~~, wherein the migraine is episodic migraine or chronic migraine.

~~3617.~~ A method for ~~assessing the quality of preparing a pharmaceutical formulation comprising~~ an erenumab composition, ~~the method~~ comprising:

~~(i) obtaining a partially purified composition comprising an erenumab composition that contains erenumab and one or more erenumab isomerization and deamidation variants, wherein erenumab comprises two heavy chains and two light chains, each said heavy chain having a sequence of SEQ ID NO: 1 or SEQ ID NO: 3 and each said light chain having a sequence of SEQ ID NO: 2 or SEQ ID NO: 4;~~

~~(ii) measuring the amount of one or more erenumab the isomerization and deamidation variants in the partially purified composition using HIC-HPLC, wherein the isomerization variant has an isoaspartic acid residue or a succinimide at amino acid position 105 in either or both heavy chains of erenumab and the deamidation variant has an aspartic acid residue, a succinimide, or an isoaspartic acid residue at amino acid position 102 in either or both heavy chains of erenumab; erenumab variants comprise isomerization variants, deamidation variants, acidic variants, HMW species, or combinations thereof;~~

~~(iii) comparing the measured amount of the one or more erenumab isomerization and deamidation variants to a pre-determined reference criterion, wherein the pre-determined reference criterion is a range from 1% to 10%; and~~

~~(iv) combining the erenumab composition with one or more excipients to preparing prepare a the pharmaceutical formulation or pharmaceutical product of the erenumab composition if the comparison indicates that the pre-determined reference criterion is met.~~

~~37.—The method of claim 36, wherein the amount of isomerization variants and deamidation variants is measured and the pre-determined reference criterion is about 10% or less.~~

~~38.—The method of claim 37, wherein the amount of isomerization variants and deamidation variants in the erenumab composition is measured by HIC-HPLC.~~

~~39.—The method of claim 36, wherein the amount of acidic variants is measured and the pre-determined reference criterion is about 38% or less.~~

~~40. The method of claim 39, wherein the amount of acidic variants in the erenumab composition is measured by CEX-HPLC.~~

~~41. The method of claim 36, wherein the amount of HMW species is measured and the pre-determined reference criterion is about 2.5% or less.~~

~~42. The method of claim 41, wherein the amount of HMW species is measured by SE-UHPLC.~~

18. The method of claim 17, wherein if the comparison in step (iii) indicates that the pre-determined reference criterion is not met, the method further comprises subjecting the erenumab composition to hydrophobic interaction chromatography to reduce the amount of the isomerization and deamidation variants to meet the pre-determined reference criterion to produce a reprocessed erenumab composition and subsequently combining the reprocessed erenumab composition with one or more excipients to prepare the pharmaceutical formulation.

19. The method of claim 17 or 18, wherein the pre-determined reference criterion is a range from 1% to 4%.

20. The method of any one of claims 17 to 19, wherein the partially purified composition is an elution pool from a cation exchange chromatography material.

4321. The method of any one of claims ~~36-17~~ to ~~4219~~, wherein the partially purified composition is a cell culture harvest ~~erenumab composition is obtained~~ from a Chinese Hamster Ovary (CHO) cell line that recombinantly expresses a nucleic acid encoding a heavy chain of SEQ ID NO: 1 and a nucleic acid encoding a light chain of SEQ ID NO: 2.

22. The method of any one of claims 17 to 21, wherein each heavy chain of erenumab has the sequence of SEQ ID NO: 3 and each light chain of erenumab has the sequence of SEQ ID NO: 4.

23. The method of any one of claims 17 to 22, wherein the one or more excipients combined with the erenumab composition include acetate, sucrose, and polysorbate.