

CLAIMS

1. An isolated human, humanized or chimeric IL-18 antibody or antibody fragment for use in the treatment and/or prevention of atopic dermatitis in a subject in need thereof, wherein the IL-18 antibody or antibody fragment comprises: a heavy chain variable region H-CDR1 comprising SEQ ID NO: 3, a heavy chain variable region H-CDR2 comprising SEQ ID NO: 9, a heavy chain variable region H-CDR3 comprising SEQ ID NO: 5, a light chain variable region L-CDR1 comprising SEQ ID NO: 6, a light chain variable region L-CDR2 comprising SEQ ID NO: 7, and a light chain variable region L-CDR3 comprising SEQ ID NO: 8.
2. The IL-18 antibody or antibody fragment for use according to claim 1, wherein the IL-18 antibody or antibody fragment specifically binds IL-18, and wherein the IL-18 antibody or antibody fragment does not bind the IL-18/IL-18 binding protein (IL-18 BP) complex.
3. The IL-18 antibody or antibody fragment for use according to any one of the preceding claims, wherein the IL-18 antibody or antibody fragment binds human IL-18 with a dissociation constant (KD) of 100 pM or less, e.g., 50 pM or less, 25 pM or less, 10 pM or less, 5 pM or less, preferably with a KD of 0.5 pM to 20 pM, in particular as measured by SET.
4. The IL-18 antibody or antibody fragment for use according to any one of the preceding claims, wherein the IL-18 antibody or antibody fragment inhibits IL-18-induced interferon gamma (IFN- γ) production from KG-1 cells with IC₅₀ of less than 5 nM, e.g., 0.1 to 1 nM.
5. The IL-18 antibody or antibody fragment for use according to any one of the preceding claims, wherein the antibody or the antibody fragment inhibits IL-18-induced interferon gamma (IFN- γ) production in whole blood with IC₅₀ of less than

150 nM, e.g., 5 to 10 nM.

- 5 6. The IL-18 antibody or antibody fragment for use according to any of the preceding claims, wherein IL-18 antibody or antibody fragment comprises a heavy chain variable domain comprising SEQ ID NO: 14 or a sequence at least 90% identical thereto; and a light chain variable domain comprising SEQ ID NO: 16 or a sequence at least 90% identical thereto.
- 10 7. The IL-18 antibody or antibody fragment for use according to claim 6, wherein the IL-18 antibody or antibody fragment comprises a mutation in the heavy chain framework, wherein the amino acid asparagine at position 30 is replaced with lysine (N30K; numbering according to Kabat).
- 15 8. The IL-18 antibody or antibody fragment for use according to any one of the preceding claims, wherein the IL-18 antibody or antibody fragment comprises a heavy chain comprising SEQ ID NO: 43 or a sequence at least 90% identical thereto; and a light chain comprising SEQ ID NO: 45 or a sequence at least 90% identical thereto.
- 20 9. The IL-18 antibody or antibody fragment for use according to any one of the preceding claims, wherein the treatment results in an improvement in an atopic dermatitis-associated parameter and wherein the improvement in the atopic dermatitis-associated parameter is selected from the group consisting of:
 - (a) a decrease from baseline in Investigator's Global Assessment (IGA) score;
 - (b) a decrease from baseline in Dermatology Life Quality Index (DLQI);
 - 25 (c) a decrease from baseline in a patient global impression of severity (PGIS);
 - (d) a decrease from baseline in a patient global impression of change (PGIC);
 - (e) a decrease from baseline in Eczema Area and Severity Index (EASI) score; and
 - (f) a decrease from baseline in Pruritus Numeric Rating Scale (NRS) score.
- 30 10. The IL-18 antibody or antibody fragment for use according to claim 9, wherein the treatment results in an improvement in an atopic dermatitis-associated parameter and

wherein the improvement in the atopic dermatitis-associated parameter is selected from the group consisting of:

(a) a decrease from baseline in Investigator's Global Assessment (IGA) score by at least by 2 points, in particular a decrease from baseline in IGA score by at least by 2 points and clear or almost clear status;

(b) a decrease from baseline in Dermatology Life Quality Index (DLQI) of at least 30%, preferably at least 40%;

(c) an improvement from baseline in a patient global impression of severity (PGIS) by at least 1 point;

(d) an improvement from baseline in a patient global impression of change (PGIC) by at least 1 point;

(e) a decrease from baseline in Eczema Area and Severity Index (EASI) score of at least 50%;

(f) percent responders with $\geq 50\%$ improvement in EASI (EASI50);

(g) percent responders with $\geq 75\%$ improvement in EASI (EASI75);

(h) percent responders with $\geq 90\%$ improvement in EASI (EASI90);

(i) percent responders with $\geq 100\%$ improvement in EASI (EASI100);

(j) a decrease from baseline in Pruritus Numeric Rating Scale (NRS) score by at least 3 points, preferably by at least 4 points.

11. The IL-18 antibody or antibody fragment for use according to any one of the preceding claims, wherein the atopic dermatitis is moderate-to-severe atopic dermatitis.

12. The IL-18 antibody or antibody fragment for use according to claim 11, wherein the moderate to severe atopic dermatitis is characterized by (i) an Investigator's Global Assessment (IGA) score of 3 or 4, and /or (ii) an Eczema Area and Severity Index (EASI) score of at least 10, particularly at least 12.

13. The IL-18 antibody or antibody fragment for use according to any one of the preceding claims, wherein the atopic dermatitis is accompanied by an infection or

wherein the related condition is an infection, in particular a skin infection, more particularly a skin superinfection.

- 5 14. The IL-18 antibody or antibody fragment for use according to claim 13, wherein the infection is (i) a bacterial infection, e.g., staphylococcal bacteria, such as Staphylococcus (S.) aureus, or streptococcal bacteria, such as Streptococcus (S.) epidermitis, and / or (ii) a viral infection, e.g., herpes viral infection.
- 10 15. The IL-18 antibody or antibody fragment for use according to any one of the preceding claims, wherein the subject did not adequately respond to a treatment with a topical atopic dermatitis therapy.
- 15 16. The IL-18 antibody or antibody fragment for use according to any one of the preceding claims, wherein the subject was refractory to topical atopic dermatitis therapy or the subject did not adequately respond to a treatment with a topical atopic dermatitis therapy.
- 20 17. The IL-18 antibody or antibody fragment for use according to claim 15 or 16, wherein the topical atopic dermatitis therapy is selected from the group consisting of topical steroid, e.g., corticosteroid, tacrolimus, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, apremilast, calcineurin inhibitor, e.g., topical calcineurin inhibitor, phosphodiesterase 4 (PDE4) inhibitor, e.g., topical PDE4 inhibitor, e.g. Crisaborole, adrenocorticotrophic hormone analogs.
- 25 18. The IL-18 antibody or antibody fragment for use according to claim 17, wherein the topical steroid is selected from the group consisting of a group I topical corticosteroid (TCS), group II topical corticosteroid (TCS) and group III topical corticosteroid (TCS).
- 30 19. The IL-18 antibody or antibody fragment for use according to claim 17, wherein the topical corticosteroid (TCS) is selected from the group consisting of

methylprednisolone aceponate, mometasone furoate, fluticasone propionate, betamethasone valerate and hydrocortisone butyrate.

20. The IL-18 antibody or antibody fragment for use according to any one of the preceding claims, wherein the IL-18 antagonist is to be administered subcutaneously or intravenously to a subject in need thereof.

21. The IL-18 antibody or antibody fragment for use according to any one of the preceding claims, wherein the IL-18 antagonist is to be administered at a dose sufficient to achieve a therapeutically effective serum level.

22. The IL-18 antibody or antibody fragment for use according to claim 21, wherein the serum level is maintained during the treatment course.

23. The IL-18 antibody or antibody fragment for use according to any one of the preceding claims, wherein the IL-18 antibody or antibody fragment is to be administered once a week, once every two weeks, once every three weeks, once every four weeks, once every eight weeks, once every 12 weeks, in particular once every 4 weeks.

24. The IL-18 antibody or antibody fragment for use according to any one of the preceding claims, wherein a second therapeutic agent is to be administered to the subject before, after, or concurrent with the IL-18 antagonist of any one of claims 1 to 8.

25. The IL-18 antibody or antibody fragment for use according to claim 24, wherein the second therapeutic agent is selected from the group consisting of steroid, cyclosporine, tacrolimus, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, apremilast, calcineurin inhibitor, e.g., topical calcineurin inhibitor, phosphodiesterase 4 (PDE4) inhibitor, e.g., topical PDE4 inhibitor, e.g. Crisaborole, adrenocorticotrophic

hormone analogs, dupilumab, etanercept, adalimumab, infliximab, omalizumab, secukinumab.

- 5 26. The IL-18 antibody or antibody fragment for use according to claim 24, wherein the second therapeutic agent is a low to medium potency steroid, e.g., topical or oral steroid, e.g., corticosteroid.
- 10 27. The IL-18 antibody or antibody fragment for use according to claim 26, wherein the second therapeutic agent is selected from the group consisting of a group I topical corticosteroid (TCS), group II topical corticosteroid (TCS) and group III topical corticosteroid (TCS).
- 15 28. The IL-18 antibody or antibody fragment for use according to claim 26, wherein the topical corticosteroid (TCS) is selected from the group consisting of methylprednisolone aceponate, mometasone furoate, fluticasone propionate, betamethasone valerate and hydrocortisone butyrate.
- 20 29. Use of an isolated human, humanized or chimeric IL-18 antibody or antibody fragment for the manufacture of a medicament for treatment and/or prevention of atopic dermatitis in a subject in need thereof, wherein the IL-18 antibody or antibody fragment comprises: a heavy chain variable region H-CDR1 comprising SEQ ID NO: 3, a heavy chain variable region H-CDR2 comprising SEQ ID NO: 9, a heavy chain variable region H-CDR3 comprising SEQ ID NO: 5, a light chain variable region L-CDR1 comprising SEQ ID NO: 6, a light chain variable region L-CDR2 comprising SEQ ID NO: 7, and a light chain variable region L-CDR3 comprising SEQ ID NO: 8.
- 25 30. The use according to claim 29, wherein the IL-18 antibody or antibody fragment specifically binds IL-18, and wherein the IL-18 antibody or antibody fragment does not bind the IL-18/IL-18 binding protein (IL-18 BP) complex.
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31. The use according to claim 29 or claim 30, wherein the IL-18 antibody or antibody fragment binds human IL-18 with a dissociation constant (KD) of 100 pM or less, e.g., 50 pM or less, 25 pM or less, 10 pM or less, 5 pM or less, preferably with a KD of 0.5 pM to 20 pM, in particular as measured by SET.

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32. The use according to any one of claims 29 to 31 wherein the IL-18 antibody or antibody fragment inhibits IL-18-induced interferon gamma (IFN- γ) production from KG-1 cells with IC50 of less than 5 nM, e.g., 0.1 to 1 nM.

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33. The use according to any one of claims 29 to 32, wherein the IL-18 antibody or antibody fragment inhibits IL-18-induced interferon gamma (IFN- γ) production in whole blood with IC50 of less than 150 nM, e.g., 5 to 10 nM.

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34. The use according to any one of claims 29 to 33, wherein the IL-18 antibody or antibody fragment comprises a heavy chain variable domain comprising SEQ ID NO: 14 or a sequence at least 90% identical thereto; and a light chain variable domain comprising SEQ ID NO: 16 or a sequence at least 90% identical thereto.

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35. The use according to claim 34, wherein the IL-18 antibody or antibody fragment comprises a mutation in the heavy chain framework, wherein the amino acid asparagine at position 30 is replaced with lysine (N30K; numbering according to Kabat).

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36. The use according to any one of claims 29 to 35, wherein the IL-18 antibody or antibody fragment comprises a heavy chain comprising SEQ ID NO: 43 or a sequence at least 90% identical thereto; and a light chain comprising SEQ ID NO: 45 or a sequence at least 90% identical thereto.

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37. The use according to any one of claims 29 to 36, wherein the treatment results in an improvement in an atopic dermatitis-associated parameter and wherein the

improvement in the atopic dermatitis-associated parameter is selected from the group consisting of:

- (a) a decrease from baseline in Investigator's Global Assessment (IGA) score;
- (b) a decrease from baseline in Dermatology Life Quality Index (DLQI);
- (c) a decrease from baseline in a patient global impression of severity (PGIS);
- (d) a decrease from baseline in a patient global impression of change (PGIC);
- (e) a decrease from baseline in Eczema Area and Severity Index (EASI) score; and
- (f) a decrease from baseline in Pruritus Numeric Rating Scale (NRS) score.

38. The use according to claim 37, wherein the treatment results in an improvement in an atopic dermatitis-associated parameter and wherein the improvement in the atopic dermatitis-associated parameter is selected from the group consisting of:

- (a) a decrease from baseline in Investigator's Global Assessment (IGA) score by at least by 2 points, in particular a decrease from baseline in IGA score by at least by 2 points and clear or almost clear status;
- (b) a decrease from baseline in Dermatology Life Quality Index (DLQI) of at least 30%, preferably at least 40%;
- (c) an improvement from baseline in a patient global impression of severity (PGIS) by at least 1 point;
- (d) an improvement from baseline in a patient global impression of change (PGIC) by at least 1 point;
- (e) a decrease from baseline in Eczema Area and Severity Index (EASI) score of at least 50%;
- (f) percent responders with $\geq 50\%$ improvement in EASI (EASI50);
- (g) percent responders with $\geq 75\%$ improvement in EASI (EASI75);
- (h) percent responders with $\geq 90\%$ improvement in EASI (EASI90);
- (i) percent responders with $\geq 100\%$ improvement in EASI (EASI100);
- (j) a decrease from baseline in Pruritus Numeric Rating Scale (NRS) score by at least 3 points, preferably by at least 4 points.

39. The use according to any one of claims 29 to 38, wherein the atopic dermatitis is moderate-to-severe atopic dermatitis.
- 5 40. The use according to claim 39, wherein the moderate to severe atopic dermatitis is characterized by (i) an Investigator's Global Assessment (IGA) score of 3 or 4, and /or (ii) an Eczema Area and Severity Index (EASI) score of at least 10, in particular at least 10.
- 10 41. The use according to any one of claims 29 to 40, wherein the atopic dermatitis is accompanied by an infection or wherein the related condition is an infection, in particular a skin infection, more particularly a skin superinfection.
- 15 42. The use according to claim 41, wherein the infection is (i) a bacterial infection, e.g., staphylococcal bacteria, such as Staphylococcus (S.) aureus, or streptococcal bacteria, such as Streptococcus (S.) epidermitis, and / or (ii) a viral infection, e.g., herpes viral infection.
- 20 43. The use according to any one of claims 29 to 42, wherein the subject did not adequately respond to a treatment with a topical atopic dermatitis therapy.
- 25 44. The use according to any one of claims 29 to 43, wherein the subject was refractory to a topical atopic dermatitis therapy or the subject did not adequately respond to a treatment with a topical atopic dermatitis therapy.
- 30 45. The use according to claim 43 or 44, wherein the topical atopic dermatitis therapy is selected from the group consisting of topical steroid, e.g., corticosteroid, tacrolimus, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, apremilast, calcineurin inhibitor, e.g., topical calcineurin inhibitor, phosphodiesterase 4 (PDE4) inhibitor, e.g., topical PDE4 inhibitor, e.g. Crisaborole, adrenocorticotrophic hormone analogs.

46. The use according to claim 45, wherein the topical steroid is selected from the group consisting of a group I topical corticosteroid (TCS), group II topical corticosteroid (TCS) and group III topical corticosteroid (TCS).
- 5 47. The use according to claim 46, wherein the topical corticosteroid (TCS) is selected from the group consisting of methylprednisolone aceponate, mometasone furoate, fluticasone propionate, betamethasone valerate and hydrocortisone butyrate.
- 10 48. The use according to any one of claims 29 to 47, wherein the IL-18 antibody or antibody fragment is to be administered subcutaneously or intravenously to a subject in need thereof.
- 15 49. The use according to any one of claims 29 to 48, wherein the IL-18 antibody or antibody fragment is to be administered at a dose sufficient to achieve a therapeutically effective serum level.
50. The use according to claim 49, wherein the serum level is maintained during the treatment course.
- 20 51. The use according to any one of claims 29 to 50, wherein the IL-18 antibody or antibody fragment is to be administered once a week, once every two weeks, once every three weeks, once every four weeks, once every eight weeks, once every 12 weeks, in particular once every 4 weeks.
- 25 52. The use according to any one of claims 29 to 51, wherein a second therapeutic agent is to be administered to the subject before, after, or concurrent with the use of the IL-18 antibody or fragment according to claims 29 to 36.
- 30 53. The use according to claim 52, wherein the second therapeutic agent is selected from the group consisting of steroid, cyclosporine, tacrolimus, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, apremilast, calcineurin inhibitor,

e.g., topical calcineurin inhibitor, phosphodiesterase 4 (PDE4) inhibitor, e.g., topical PDE4 inhibitor, e.g. Crisaborole, adrenocorticotrophic hormone analogs, dupilumab, etanercept, adalimumab, infliximab, omalizumab, secukinumab.

5 54. The use according to claim 52, wherein the second therapeutic agent is a low to medium potency steroid, e.g., topical or oral steroid, e.g., corticosteroid.

10 55. The use according to claim 52, wherein the second therapeutic agent is selected from the group consisting of a group I topical corticosteroid (TCS), group II topical corticosteroid (TCS) and group III topical corticosteroid (TCS).

15 56. The use according to claim 52, wherein the topical corticosteroid (TCS) is selected from the group consisting of methylprednisolone aceponate, mometasone furoate, fluticasone propionate, betamethasone valerate and hydrocortisone butyrate.