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Datasheet for the decision of 17 June 2025

Case Number: T 0709/23 - 3.3.04

Application Number: 17168574.6

Publication Number: 3219729

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Language of the proceedings: EN

Title of invention:
Interleukin-31 monoclonal antibody

Patent Proprietor:
Zoetis Services LLC

Opponents:
Margaret Dixon Limited
Boehringer Ingelheim Vetmedica GmbH

Headword:
Anti-IL-31 in cats/ZOETIS SERVICES

Relevant legal provisions:
EPC Art. 83

Keyword:
Sufficiency of disclosure - (no)

Decisions cited:
G 0002/21, T 0609/02

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Case Number: T 0709/23 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 17 June 2025

Appellant: (Patent Proprietor)	Zoetis Services LLC 10 Sylvan Way Parsippany, NJ 07054 (US)
Representative:	Cornwell, Matthew James Zoetis The Glenn Berge Building Babraham Research Campus Babraham, Cambridge CB22 3FH (GB)
Respondent I: (Opponent 1)	Margaret Dixon Limited 1st Floor, Aurora Building Counterslip Bristol BS1 6BX (GB)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Respondent II: (Opponent 2)	Boehringer Ingelheim Vetmedica GmbH Binger Straße 173 55216 Ingelheim am Rhein (DE)
Representative:	D Young & Co LLP 3 Noble Street London EC2V 7BQ (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 20 February 2023 revoking European patent No. 3 219 729 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

Chairman	L. Bühler
Members:	O. Lechner
	B. Rutz

Summary of Facts and Submissions

I. The patent proprietor (appellant) filed an appeal against the opposition division's decision to revoke European patent No. 3 219 729.

II. The patent was granted on European patent application No. 17 168 574.6, which is a divisional application of European patent application No. 12 748 547.2. The latter was filed as an international application under the PCT published as WO 2013/011407 (earlier application as filed).

III. In its decision, the opposition division decided that none of the requests on file - the main request or auxiliary requests 1 to 20 - met the requirements of Article 83 EPC.

IV. With its statement of grounds of appeal, the appellant resubmitted sets of claims according to a main request and auxiliary request 1 to 20 (as dealt with in the decision under appeal) and provided arguments why the claimed subject-matter complied with the requirements of Article 83 EPC and Articles 54, 56, 84, 76(1) and 123(2) EPC. The appellant also submitted new documents D56 and D57.

V. Opponents 1 and 2 (respondents I and II) replied to the statement of grounds of appeal.

VI. The appellant submitted further arguments together with new documents D58 to D60, to which Respondent II replied.

VII. The board summoned the parties to oral proceedings as requested.

VIII. All parties submitted a further letter each.

IX. In the communication of the board pursuant to Article 15(1) RPBA, the board set out its preliminary opinion on several issues.

X. All parties replied to the communication. The appellant requested that the current appeal proceedings be stayed pending further guidance from the Enlarged Board of Appeal in the written decision in case G 1/24, concerning the standard for claim interpretation.

XI. Oral proceedings before the board took place on 17 June 2025.

During the oral proceedings, the appellant filed a new auxiliary request 1, which was subsequently withdrawn. The initial main request and auxiliary requests 1 to 20 were maintained.

At the end of the oral proceedings, the Chair announced the board's decision.

XII. Claim 1 as granted of the main request and of auxiliary requests 1 to 20 reads (amendments compared to claim 1 as granted highlighted by the board):

Claim 1 as granted
"1. An isolated antibody that specifically binds to feline IL-31, wherein said antibody reduces, inhibits or neutralizes feline IL-31-mediated pSTAT signaling in a cell based assay."

Main request
"1. An isolated antibody that specifically binds to feline IL-31, wherein said antibody reduces, inhibits or neutralizes feline IL-31-mediated pSTAT signaling in a cell based assay, for use in treating a pruritic condition or an allergic condition in cats."

Auxiliary request 1
"1. An isolated antibody that specifically binds to feline IL-31, wherein said antibody reduces, inhibits or neutralizes feline IL-31-mediated pSTAT signaling in a cell based assay, for use in treating a pruritic condition in cats."

Auxiliary request 2
"1. An isolated antibody that specifically binds to feline IL-31, wherein said antibody reduces, inhibits or neutralizes feline IL-31-mediated pSTAT signaling in a cell based assay, for use in treating a pruritic condition in cats, wherein the pruritic condition is atopic dermatitis."

Auxiliary request 3
"1. An isolated antibody that specifically binds to feline IL-31, wherein said antibody ~~reduces,~~ inhibits ~~or neutralizes~~ feline IL-31-mediated pSTAT signaling in a cell based assay, for use in treating a pruritic condition or an allergic condition in cats, and wherein the antibody is felinized."

Auxiliary request 4
"1. An isolated antibody that specifically binds to feline IL-31, wherein said antibody ~~reduces,~~ inhibits ~~or neutralizes~~ feline IL-31-mediated pSTAT signaling in a cell based assay, for use in treating a pruritic

condition in cats, and wherein the antibody is felinized."

Auxiliary request 5
"1. An isolated antibody that specifically binds to feline IL-31, wherein said antibody ~~reduces, inhibits or neutralizes~~ feline IL-31-mediated pSTAT signaling in a cell based assay, for use in treating a pruritic condition in cats, wherein the pruritic condition is atopic dermatitis, and wherein the antibody is felinized."

Auxiliary request 6
"1. An isolated antibody that specifically binds to feline IL-31, wherein said antibody ~~reduces, inhibits or neutralizes~~ feline IL-31-mediated pSTAT signaling in a cell based assay, for use in treating a pruritic condition in cats, wherein the pruritic condition is atopic dermatitis, wherein the antibody is felinized and specifically binds to a region on feline IL-31 that corresponds to a region between amino acid residues 95 and 125 of the canine IL-31 amino acid sequence of SEQ ID NO: 32."

Auxiliary request 7
"1. An isolated antibody that specifically binds to feline IL-31, wherein said antibody reduces, inhibits or neutralizes ~~feline~~cat IL-31-mediated pSTAT signaling in a cell based assay, for use in treating a pruritic condition or an allergic condition in cats."

Auxiliary request 8
"1. An isolated antibody that specifically binds to feline IL-31, wherein said antibody reduces, inhibits or neutralizes ~~feline~~cat IL-31-mediated pSTAT signaling

in a cell based assay, for use in treating a pruritic condition in cats."

Auxiliary request 9
"1. An isolated antibody that specifically binds to feline IL-31, wherein said antibody reduces, inhibits or neutralizes ~~feline~~cat IL-31-mediated pSTAT signaling in a cell based assay, for use in treating a pruritic condition in cats, wherein the pruritic condition is atopic dermatitis."

Auxiliary request 10
"1. An isolated antibody that specifically binds to feline IL-31, wherein said antibody ~~reduces, inhibits or neutralizes~~ ~~feline~~cat IL-31-mediated pSTAT signaling in a cell based assay, for use in treating a pruritic condition or an allergic condition in cats, and wherein the antibody is felinized."

Auxiliary request 11
"An isolated antibody that specifically binds to feline IL-31, wherein said antibody ~~reduces, inhibits or neutralizes~~ ~~feline~~cat IL-31-mediated pSTAT signaling in a cell based assay, for use in treating a pruritic condition in cats, and wherein the antibody is felinized."

Auxiliary request 12
"An isolated antibody that specifically binds to feline IL-31, wherein said antibody ~~reduces, inhibits or neutralizes~~ ~~feline~~cat IL-31-mediated pSTAT signaling in a cell based assay, for use in treating a pruritic condition in cats, wherein the pruritic condition is atopic dermatitis, and wherein the antibody is felinized."

Auxiliary request 13
"An isolated antibody that specifically binds to feline IL-31, wherein said antibody ~~reduces, ~~inhibits~~ or neutralizes feline~~cat IL-31-mediated pSTAT signaling in a cell based assay, for use in treating a pruritic condition in cats, wherein the pruritic condition is atopic dermatitis, wherein the antibody is felinized and specifically binds to a region on feline IL-31 that corresponds to a region between amino acid residues 95 and 125 of the canine IL-31 amino acid sequence of SEQ ID NO: 32.

Auxiliary request 14
"1. An isolated antibody that specifically binds to feline IL-31, wherein said antibody reduces, inhibits or neutralizes ~~feline IL-31 mediated~~ pSTAT signaling mediated by IL-31 of SEQ ID NO: 70 in a cell based assay, for use in treating a pruritic condition or an allergic condition in cats."

Auxiliary request 15
"1. An isolated antibody that specifically binds to feline IL-31, wherein said antibody reduces, inhibits or neutralizes ~~feline IL-31 mediated~~ pSTAT signaling mediated by IL-31 of SEQ ID NO: 70 in a cell based assay, for use in treating a pruritic condition in cats."

Auxiliary request 16
"1. An isolated antibody that specifically binds to feline IL-31, wherein said antibody reduces, inhibits or neutralizes ~~feline IL-31 mediated~~ pSTAT signaling mediated by IL-31 of SEQ ID NO: 70 in a cell based assay, for use in treating a pruritic condition in cats, wherein the pruritic condition is atopic dermatitis."

Auxiliary request 17
"1. An isolated antibody that specifically binds to feline IL-31, wherein said antibody ~~reduces, inhibits or neutralizes feline IL-31 mediated~~ pSTAT signaling mediated by IL-31 of SEQ ID NO: 70 in a cell based assay, for use in treating a pruritic condition or an allergic condition in cats, and wherein the antibody is felinized."

Auxiliary request 18
"1. An isolated antibody that specifically binds to feline IL-31, wherein said antibody ~~reduces, inhibits or neutralizes feline IL-31 mediated~~ pSTAT signaling mediated by IL-31 of SEQ ID NO: 70 in a cell based assay, for use in treating a pruritic condition in cats, and wherein the antibody is felinized."

Auxiliary request 19
"1. An isolated antibody that specifically binds to feline IL-31, wherein said antibody ~~reduces, inhibits or neutralizes feline IL-31 mediated~~ pSTAT signaling mediated by IL-31 of SEQ ID NO: 70 in a cell based assay, for use in treating a pruritic condition in cats, wherein the pruritic condition is atopic dermatitis, and wherein the antibody is felinized."

Auxiliary request 20
"1. An isolated antibody that specifically binds to feline IL-31, wherein said antibody ~~reduces, inhibits or neutralizes feline IL-31 mediated~~ pSTAT signaling mediated by IL-31 of SEQ ID NO: 70 in a cell based assay, for use in treating a pruritic condition in cats, wherein the pruritic condition is atopic dermatitis, wherein the antibody is felinized and

specifically binds to a region on feline IL-31 that corresponds to a region between amino acid residues 95 and 125 of the canine IL-31 amino acid sequence of SEQ ID NO: 32."

XIII. Reference is made to the following documents:

D37: EMBOSS Needle - Alignment of dog (SEQ ID NO: 32) and cat (SEQ ID NO: 70) IL-31

D38: J. Scheerlinck, Vet Immunol Immunopathol 72(1-2), 1999, 39-44

D39: M. Wisselink and T. Willemse, Vet J 180(1), 2009, 55-9

D46: Q. Zhang et al., Cytokine Growth Factor Rev 19(5-6), 2008, 347-56

D51: WO 2019/177697 A2

D60: S. Paterson, "Manual of Skin Diseases of the Dog and Cat", 2nd edn., John Wiley & Sons, 2008, 178 and 184

XIV. The appellant's arguments relevant to the decision are summarised as follows.

Main request

Disclosure of the invention as claimed - Article 83 EPC

Claim 1 defined the antibodies by three functional properties: i) the ability to bind to feline IL-31, ii) to reduce, inhibit or neutralise feline IL-31-mediated

pSTAT signalling in a cell-based assay, and iii) the capacity to treat a pruritic or allergic condition in cats. Antibodies not fulfilling these criteria, particularly those lacking a therapeutic effect in cats, would not fall within the scope of claim 1.

The patent provided a clear and credible teaching for implementing the invention, demonstrating that IL-31-mediated pruritus could be reduced using anti-IL-31 antibodies 11E12 and 34D03. Based on the use of similar medications in dogs and cats for atopic dermatitis (documents D39 and D60), it was known that feline and canine atopic dermatitis shared similarities, making dogs a suitable model for atopic dermatitis in cats. In line with the requirement in decisions G 2/21 (Reasons point 74) and T 609/02 (Reasons point 9), the patent rendered it credible that an antibody that specifically binds to feline IL-31 where this antibody reduces, inhibits or neutralises feline IL-31-mediated pSTAT signalling in a cell-based assay was suitable for use in treating a pruritic condition or an allergic condition in cats.

Given the close phylogenetic relationship and functional similarity of IL-31 of dogs and cats (documents D37, D38 and D46), it was credible that antibodies effective in dogs would also be effective in cats. The patent demonstrated that feline IL-31 activates pSTAT signalling in canine DH-82 cells with similar potency to canine IL-31. It also showed that antibodies targeting a conserved epitope on IL-31 shared by cats and dogs were effective in dogs. This was supported by a 75% overall sequence identity between feline and canine IL-31 (document D37) and by document D38, which suggested that cytokines with over 60% identity often cross-reacted.

On this basis, the data in document D51, which included further antibodies developed using the patent's screening method, could be regarded as complementary to the patent's teaching.

The teaching of the patent was not limited to antibodies binding to the same region described for 11E12 and 34D03. Rather, it provided clear instructions on how to arrive at the claimed invention without undue burden. The binding region for antibodies 11E12 and 34D03 was conserved across dogs and cats, and the lack of efficacy of the low-affinity, low-potency antibody 11E12 1.1 at a low dose did not undermine the patent's therapeutic concept. Additionally, the mouse:feline 11E12 antibody reduced pruritus in cats at day 0 by 20% (Figure 9, D51), and the lack of statistical significance was deemed immaterial.

Even if the two 11E12-derived antibodies tested in document D51 were considered not to show significant therapeutic effect in cats, occasional failures did not impair reproducibility if only a few attempts were needed to achieve success (Case Law of the Boards of Appeal, 10th edn., 2022, II.C.6.6.1). In certain fields, such as biotechnology, occasional failure had to be regarded as the rule rather than the exception.

Following the patent, the skilled person needed to produce anti-IL-31 antibodies and select those capable of reducing, inhibiting or neutralising feline IL-31-mediated pSTAT signalling in a cell-based assay, i.e. those capable of inhibiting the interaction between IL-31 and its receptor. There was no need to know the antibody's epitope. The pSTAT assay served as a useful indicator for preselecting antibodies capable of inhibiting IL-31 receptor interaction and had also been

used for this purpose in document D51. Of course, not all anti-IL-31 antibodies inhibiting pSTAT signalling *in vitro* would necessarily show therapeutic effect.

Contrary to the respondents' argument, document D51 did not abandon antibody 11E12 or consider it hopeless. Page 110, lines 14 ff of document D51 showed that the inventors considered optimisation of antibody 11E12, as was done for antibody 15H05. Based on the initial 20% reduction in pruritus observed for antibody 11E12 in Figure 9 of document D51 at study day 0, the skilled person would have sought to improve efficacy, for example, by increasing the dose or modifying the antibody. Document D51 focused on the novel IL-31 binding site of antibody 15H05 to render the application patentable over prior art such as the patent in suit.

While the patent showed an *in vivo* therapeutic effect in dogs, it did not provide *in vivo* data in cats. However, as evidenced by document D51, following the credible technical concept and road map provided in the patent, it was possible to identify anti-IL-31 antibodies successful in treating pruritus in cats.

XV. The respondents' arguments relevant to the decision are summarised as follows.

Main request

Disclosure of the invention as claimed - Article 83 EPC

The patent did not provide a sufficient rationale for assuming cross-species efficacy. The suggestion that antibodies effective in dogs might also work in cats

lacked the experimental support necessary to render it credible. Mere assertions were inadequate; the patent should have included either data or a sound scientific rationale for the claimed therapeutic effect in cats. The extrapolation from dogs to cats remained speculative and unsupported. Documents D38, D39, D46, and D60 did not provide conclusive evidence for the appellant's position. Although canine and feline IL-31 shared relatively high sequence identity, this alone was insufficient to establish therapeutic equivalence.

Crucially, document D51 showed that the 11E12 antibody, which was central to the patent, failed to demonstrate therapeutic efficacy in cats, despite binding to the same conserved epitope in dogs. The patent therefore did not render the claimed effect plausible, and serious doubts remained, substantiated by verifiable facts, undermining sufficiency under Article 83 EPC.

The patent did not provide sufficient guidance to enable the skilled person to carry out the invention without undue burden, particularly across the full breadth of the claims. The claims were defined solely by functional features — binding to feline IL-31, inhibiting pSTAT signalling and treating pruritic or allergic conditions in cats — without any structural limitations.

Document D51 provided serious doubts, showing that the cross-reactive antibody 11E12 failed to achieve a significant therapeutic effect in cats. This demonstrated that following the patent's teaching would lead to failure. To overcome this failure, the skilled person had to perform a research programme. The appellant could not rely on the data for other antibodies in document D51, such as antibody 15H05 and

its derivative ZTS-361, as they were not disclosed in the patent and bound to a different IL-31 region, also not disclosed in the patent.

As shown in document D51, pSTAT signalling was not a reliable predictor of therapeutic success.

XVI. The parties' requests relevant to the decision were as follows.

(a) The appellant requested that the decision under appeal be set aside and the case be remitted to the opposition division for consideration of novelty and inventive step on the basis of the main request or one of auxiliary requests 1 to 20 or, alternatively, that the patent be maintained on the basis of one of these claim requests.

(b) Respondents I and II requested that the appeal be dismissed. Respondent II further requested that the case be remitted to the opposition division for consideration of novelty and inventive step, and possibly clarity, if the decision was set aside.

Reasons for the Decision

Main request

Disclosure of the invention as claimed - Article 83 EPC

1. For the assessment of the disclosure of the invention, reference is made in the following to the published application EP3219729 A1 (the patent application).

Claim construction

2. Claim 1 is drafted as a purpose-limited product claim under Article 54(5) EPC. The therapeutic indication "for use in treating a pruritic or allergic condition in cats" constitutes a functional technical feature of the claim. The antibody is defined solely by two functional features: its specific binding to feline IL-31 and its inhibition of IL-31-mediated pSTAT signalling. However, defining the antibody in terms of functional features does not, in itself, establish a credible link to the claimed therapeutic indication. These features represent an abstraction from the specific antibodies disclosed in the application and serve as a substitute for a structural definition of the therapeutic agent. The mere assertion that such functional properties enable the therapeutic effect is not sufficient. The application as filed must provide clear and direct disclosure demonstrating that the functionally defined antibody is indeed suitable for achieving the claimed therapeutic effect. This functional-therapeutic link must be derivable from the patent application.

3. In the decision under appeal (point 8) and throughout the written appeal proceedings, it was a matter of debate whether the expression "feline IL-31-mediated pSTAT signalling in a cell based assay" in claim 1 should be interpreted such that the adjective "feline" qualifies only "IL-31" or whether it also extends to "pSTAT signalling" and/or the "cell based assay".

4. For the purpose of analysing the disclosure of the invention claimed, the board adopted the interpretation proposed by the appellant, according to which the term

"feline" in claim 1 refers exclusively to IL-31 and not to the pSTAT signalling or the assay system.

Accordingly, in the following assessment, claim 1 was construed as referring to the reduction, inhibition or neutralisation of pSTAT signalling mediated by feline IL-31 in an assay using cells from an animal of any kind.

Two issues were raised under Article 83 EPC:
- whether the therapeutic effect demonstrated in dogs, as disclosed in the patent application, could be credibly extrapolated to cats
- whether the skilled person would be able to carry out the invention over the entire scope of claim 1 without undue burden

Extrapolation of therapeutic effect from dogs to cats

5. Under established case law, for the requirement of sufficiency to be met, the patent application must provide suitable evidence for the claimed therapeutic use.

6. The appellant argued that the *in vivo* dog data disclosed in the patent rendered the claimed therapeutic effect in cats credible. This was based on the close phylogenetic relationship between dogs and cats and the absence of evidence suggesting that IL-31 functioned differently in the two species.

In contrast, the respondents argued that the patent application disclosed neither *in vitro* inhibition of feline IL-31 nor *in vivo* efficacy in cats. Furthermore, post-published document D51 indicated that antibodies binding to the disclosed epitope failed to treat

pruritus in cats, casting serious doubts on whether the dog data plausibly supported the claimed therapeutic use in cats.

The parties also discussed different documents, such as D37 (dog and cat IL-31 showing 75% identity at amino acid level), D46 (dog and cat IL-31 showing 75% identity) and D39 and D60 (both showing that some of the medications used to treat atopic dermatitis in dogs are also used in cats) for the question of whether data on IL-31 in dogs could be credibly extrapolated to cats.

7. While this point was disputed, the board bases its assessment on the second objection - namely, that the claimed invention cannot be carried out across the entire scope claimed. Accordingly, it was not necessary for the board to decide whether the skilled person would have credibly extrapolated the data on IL-31 in dogs to cats. In the following, the therapeutic effect observed in dogs is assumed to be credibly achieved also in cats.

Effect over the entire scope of claim 1

8. In line with established case law, the requirements of sufficiency of disclosure are met if a person skilled in the art can carry out the claimed invention over the whole scope of the claims without undue burden using their common general knowledge. The disclosure of one way of performing an invention is only sufficient if it allows the invention to be performed in the whole range claimed rather than only for some members of the claimed class to be obtained. Where the person skilled in the art has to resort to trial-and-error experimentation to identify compounds, if any, which

meet the functional definition set out in the claim, this constitutes an undue burden, even if it involves routine experiments (Case Law of the Boards of Appeal, 10th edn., 2022, II.C.5.4, II.C.6.7, and II.C.7.1.2).

Evidence in the patent application

9. Examples 1 to 9 and 12 of the patent application relate exclusively to dogs, whereas cats are only addressed in Examples 10 and 11.

9.1 Examples 1 to 4 describe the development of mouse anti-dog IL-31 monoclonal antibodies 11E12, 19D07 and 34D03, which bind with high affinity to IL-31 and inhibit IL-31-induced signal transducer and activator of transcription protein (STAT) phosphorylation in a DH-82 canine monocyte assay.
Paragraphs [0173], lines 1 to 3 state: "*To confirm that the inhibition of IL-31-mediated cell signaling, observed in the DH-82 assay, correlates with inhibition of IL-31-mediated pruritus in the dog the chimeric 11E12 monoclonal antibody* […] *was evaluated in the IL-31 dog pruritus model*". Paragraph [0175] concludes *inter alia* that "*inhibition of IL-31 mediated signaling in the cell based assay correlates with in vivo efficacy*".

Examples 5 and 6 outline the caninisation strategy for the mouse antibodies 11E12, 19D07 and 34D03, involving grafting mouse CDRs onto canine antibody frameworks.

Example 7 investigates the binding of antibodies 11E12 and 34D03 to canine IL-31 and determines the epitope on dog IL-31 to which antibodies 11E12 and 34D03 bind (see point 10. below).

Table 3 shows that mouse and chimeric versions of the three anti-dog IL-31 antibodies show similar IC_{50} values in a DH-82 pSTAT assay and have similar dissociation constants (K_D), i.e. affinity.
Table 4 shows that while the original caninised 11E12 antibody showed a considerably lower affinity compared to the mouse parent antibody, the affinity could be restored by optimisation of the framework regions (FR; see Figure 11).

Examples 8 and 9 describe the production and *in vivo* evaluation of the caninised monoclonal antibody 34D03, showing successful expression in HEK 293 cells and significant reduction of IL-31-induced pruritic behaviour in dogs following a single subcutaneous dose.

Example 12 presents a diagnostic assay using these antibodies to detect elevated IL-31 levels in dogs with naturally occurring atopic dermatitis.
Example 12 shows that levels of IL-31 were detectable in serum samples of 57% of dogs with naturally occurring atopic dermatitis (~13 pg/ml) but were not detectable (<13 pg/ml) in the serum from purpose-bred beagles, both sensitised and non-sensitised to house dust mite allergen; mixed breed dogs, both with and without flea infestation or client-owned dogs with periodontal disease but otherwise considered in good health, regardless of breed (see paragraph [0198] of the patent application).

9.2 Examples 10 and 11 specifically address cats.
In Example 10, recombinant feline IL-31 is shown to induce STAT phosphorylation in canine DH-82 monocytes *in vitro* (Figure 19). Paragraphs [0191] and [0192] of the patent application state that: "*Alanine-scanning mutagenesis of canine IL-31 defined a region within the*

protein that is necessary for binding to the 11E12 and 34D03 antibodies. It was hypothesized, due to sequence conservation in this region (Figure 20), that these mAbs would cross-react with feline IL-31. Figure 21 shows that mAbs 11E12 and 34D03 are capable of binding to canine IL-31 (E.coli) and are also capable of cross-reacting with the feline IL-31 protein. Based on these data, speciation of the 34D03 antibody to feline (felinization) was pursued."

In Example 11, a felinised version of antibody 34D03 was engineered and shown to retain strong binding and inhibitory activity against canine and feline IL-31 *in vitro* (Figure 23). It is also stated that "*these results suggest that a conserved epitope on feline IL-31 may be a suitable target for inhibition of this cytokine in cats.*" (paragraph [0194]).

10. While the patent application shows that feline IL-31 can activate pSTAT in canine DH-82 cells (see Example 10, paragraph [0190] and Figure 19), it does not demonstrate that antibody 11E12 or 34D03 inhibits IL-31-mediated pSTAT signalling in feline cells or is effective in treating pruritic or allergic conditions in cats *in vivo*.

The patent application shows that the epitope for antibodies 11E12 and 34D03 comprises amino acids Asp99, Lys100, Ile103, Asp104 and Ile107 of the canine IL-31 full-length protein sequence of SEQ ID NO: 32 (see paragraphs [0183] to [0185]). This epitope is located within the conserved sequence stretch Ser76 to Leu91 (see paragraphs [0191] and [0194] and Figures 15, 16 and 20; which corresponds to positions Ser98 to Leu113 of SEQ ID NO: 32), leading to the hypothesis that the antibodies would cross-react with feline IL-31 (see

paragraph [0192]). This was confirmed in the patent application (see paragraph [0192] and Figure 21), leading to the suggestion that "*a conserved epitope on feline IL-31 may be a suitable target for inhibition of this cytokine in cats*" (see paragraph [0194]).

11. A person skilled in the art, attempting to carry out the invention in cats as claimed, would have followed the teaching of the patent application. They would have selected one of the few antibodies disclosed, which are described as binding to an epitope conserved between canine and feline IL-31 (see paragraphs [0185], [0191], [0192] and [0194] of the patent application) and felinised it as disclosed for antibody 34D03 in Example 11.

The appellant argued that the skilled person would have used antibody 34D03 rather than 11E12. However, the board is of the opinion that the fact that in the patent application only antibody 34D03 was caninised (Example 7), felinised (Example 11) and used in the dog pruritus model (Example 9) does not render it a more promising candidate for further development and/or testing than antibody 11E12.

The skilled person would have tested a felinised version of either of the claimed antibodies, i.e. 11E12 or 34D03 in a cell-based pSTAT signalling assay using feline cells *in vitro*, followed by *in vivo* testing in cats. This approach mirrors the methodology applied in document D51 (see point 12. below). In case of failure, the skilled person would have modified the antibody or tried to change the binding site within the conserved region identified in the patent application. However, based on the teachings in the patent application, the

skilled person would not have considered targeting a new, distinct binding site on IL-31.

In the board's view, the relevant question is not so much which antibody the skilled person would have selected as a starting point, but rather whether the skilled person could carry out the invention based on the patent application considered as a whole, and in light of common general knowledge. The skilled person would expect that each of the disclosed antibodies — i.e. both 11E12 and 34D03 — would be capable of achieving the claimed effect in cats. Whether the approach would have worked with antibody 34D03 remains speculative. What is known is that the approach did not work with antibody 11E12 (see document D51 discussed in point 12. below).

There is no evidence on file that this constitutes an isolated failure. The available data concerning one of the two claimed antibodies demonstrate that the desired effect in cats was not achieved with an antibody binding to the conserved epitope disclosed in the patent application. There is neither evidence nor any indication that this failure was exceptional or limited to 11E12.

Post-published evidence - document D51

12. Post-published document D51 (Examples 1.13 and 1.14; Figures 2A and 3) shows that mouse:feline chimeric antibodies 11E12 and 15H05 bind to feline and canine IL-31 (Figure 2A) and inhibit feline IL-31-mediated pSTAT3 signalling in canine and feline macrophages (Figure 3; page 109, last paragraph). Figure 9 of document D51 further demonstrates that while chimeric antibody 15H05 significantly reduced IL-31-induced

pruritus in cats at days 0, 7 and 21, the mouse:feline chimeric 11E12 antibody "*did not achieve a significant reduction in pruritus at any timepoint when compared to vehicle placebo*" (see also page 111, first paragraph).

Thus, an *in vivo* effect in cats is demonstrated only for antibody 15H05, which binds to a distinct epitope on IL-31 (see Figure 6B of document D51), namely between amino acid residues Ser124 and Phe135 of feline and canine IL-31 (numbering according to SEQ ID NO: 32 in the patent application and SEQ ID NOs: 155 (dog) and 157 (cat) in document D51) - an epitope newly identified in document D51 (Example 1.2 on page 88, Example 1.10 on page 105 and Example 1.11 on page 107). For the binding site of the 11E12 antibody, document D51 refers to US patent No. 8,790,651, a family member of the patent in suit (see also Figure 6b).

Document D51 emphasises in Example 1.10 on page 105 that "[k]*nowledge of the epitope on IL-31 that is recognized by an antibody is critical to understanding the mechanism by which it neutralizes the cytokine from binding to the IL-31Ra:OSMR co-receptor*".

Example 1.22 and Figure 25 of document D51 show that anti-feline IL-31 antibodies ZTS-5864 and ZTS-5865 (which bind to the newly identified epitope of document D51) inhibit IL-31-mediated pSTAT signalling in feline FCWF4 cells. Antibody ZTS-5864 also inhibits IL-31-induced pruritus in cats (Example 1.23; Figure 26).

Document D51 discusses the different findings for antibodies 11E12 and 15H05 on page 111, paragraph 2, concluding that "[t]*hese data suggest that the manner in which antibody 15H05 CDRs recognize feline IL-31 is superior at neutralizing the cytokines ability to*

signal through its co-receptor in turn making it more effective at blocking pruritus in cats".

13. The data generated in document D51 (see Example 1.13 and Figures 2, 3, and 9) using 11E12 antibody variants which bind to the conserved epitope described in the patent application (see point 10. above and Figure 6B of document D51) contradict the central teaching of the patent application that inhibition of feline IL-31-mediated pSTAT signalling correlated with therapeutic efficacy *in vivo*.

Instead, the data in document D51 (e.g. Figure 9 and page 111, first paragraph) show that an antibody targeting the conserved antigenic region on IL-31 according to the patent application (see point 10. above), while being able to inhibit feline IL-31-mediated pSTAT signalling in cat cells, failed to achieve significant therapeutic effects in cats.

This demonstrates that there is no clear correlation between the functional features of reducing, inhibiting or neutralising feline IL-31-mediated pSTAT signalling in a cell-based assay and the *in vivo* efficacy in treating a pruritic or allergic condition in cats.

Document D51 furthermore shows that this lack of correlation applies to two different 11E12 antibody variants, i.e. mouse:feline 11E12 and feline 11E12 1.1. This cannot be regarded as an occasional failure. In the absence of any data demonstrating that other antibodies targeting the same conserved region on IL-31 to which the 11E12 antibody variants bind achieve the claimed therapeutic effect, it must be assumed that this entire class of antibodies, as described in the patent, is not suitable for treating pruritus in cats.

14. As shown by document D51, additional research was necessary to arrive at an anti-IL-31 antibody capable of treating a pruritic or allergic condition in cats. Based on the data in document D51, there are serious doubts substantiated by verifiable facts whether following the teaching of the patent application a skilled person would arrive without undue burden at an antibody suitable for treating a pruritic or allergic condition in cats.

15. The appellant argued that Figure 9 of document D51 disclosed an initial trend toward pruritus reduction, namely a 20% reduction at study day 0 for the mouse:feline 11E12 chimera, from which some degree of therapeutic effect could be inferred. Page 111, lines 4 and 5 also mentioned that the mouse:feline 11E12 chimera showed an initial trend in efficacy at day 0.

16. However, the appellant's interpretation is clearly contradicted when reading the entire section on page 111, lines 4 to 8 of document D51, which states: "*Although the mouse:feline 11E12 chimera showed an initial trend in efficacy at day zero, it did not achieve a significant reduction in pruritus at any timepoint when compared to vehicle placebo. Feline 11E12 1.1 did not reduce pruritus at day zero and showed no trend in efficacy when compared to vehicle placebo* [...]"

17. The appellant also argued that the 11E12 antibody variants tested in document D51 were different to and not representative of the functional 11E12 antibody disclosed in the patent as the initial caninised version of the 11E12 antibody also lacked IL-31 binding and only regained activity when paired with a chimeric

light chain (Example 6, Figure 10 of the patent application).

The lack of efficacy observed in document D51 for the 11E12 antibody variants could be due to technical issues such as reduced affinity of the specific 11E12 antibody tested or its pharmacokinetic and/or pharmacodynamic properties following felinisation, rather than a failure of the underlying therapeutic concept.

Moreover, focusing solely on antibody 11E12 disregarded the broader technical teaching of document D51, which demonstrated that the anti-IL-31 antibody 15H05 (a chimeric mouse:feline antibody) and its derivatives ZTS-361 and ZTS-5864 effectively inhibited pSTAT signalling in a feline cell-based assay and treated pruritus in cats. Figure 3 of document D51 further showed that IC_{50} values correlated with anti-pruritic effects in cats.

18. The board notes that the mouse:feline chimeric 11E12 antibody tested in Figure 9 of document D51 exhibits approximately the same affinity for feline IL-31 ($K_D = 1.3x10^{-10}$, Figure 2)) as the original mouse 11E12 antibody ($K_D = 7.38x10^{-10}$). Moreover, it shows even greater affinity for feline IL-31 than the mouse:feline chimeric 15H05 antibody ($K_D = 6.99x10^{-9}$). In contrast, the felinised 11E12 1.1 (feline 11E12 1.1) antibody displays relatively weak affinity ($K_D = 2.22x10^{-8}$), as shown in Figure 2 of document D51.

While mouse:feline chimeric 11E12 (IC_{50} = 3.45 µg/ml) and mouse:feline chimeric 15H05 (IC_{50} = 3.25 µg/ml) show similar capacity to inhibit feline IL-31 mediated pSTAT signalling in feline FCWF4 cells (Figure 3),

feline 11E12 1.1 (IC_{50} = 4.47 µg/ml) shows only a marginally higher IC_{50}, which is within the range observed for antibody ZTS-361 (IC_{50} = 4.89 µg/ml). Importantly, while antibody 15H05 and its derivative ZTS-361 achieve a statistically significant reduction of IL-31-induced pruritus in cats (Figures 9 and 10), neither of the two 11E12 antibody variants does.

19. Given that antibodies with similar potency (IC_{50}) in the pSTAT signalling assay on feline cells show markedly different effects on pruritus in cats, it is apparent that the capacity to inhibit pSTAT signalling is not a reliable predictor of *in vivo* efficacy in reducing pruritus in cats.

20. Contrary to the appellant's line of argument, the board considers that document D51 cannot be used to complement the disclosure in the patent. Document D51 discloses that antibody 15H05, its felinised form ZTS-361 (Example 1.9) and ZTS-5864 (D51, page 127, lines 6 to 7) all bind to a region of wildtype feline IL-31 distinct from that targeted by antibodies 11E12 and 34D03 (document D51, page 106, line 22 ff; Figure 6b and point 10. above). The patent application contains no indication of any epitope located outside the conserved region identified in the patent application (Figure 20), and such knowledge represents a finding that was only made years after the filing of the patent application.

21. The central teaching of the patent application of a conserved region between dog and cat IL-31 which could be targeted by an antibody would have led to failure when aiming at providing an antibody for treating pruritus in cats. The patent application does not

provide any information on how this failure could be overcome or turned into a success.

Conclusion on the disclosure of the claimed invention

22. The patent application does not disclose the invention as defined in claim 1 of the main request in a manner sufficiently clear and complete for it to be carried out by the person skilled in the art (Article 83 EPC).

Auxiliary request 1 to 20

Disclosure of the claimed invention - Article 83 EPC

23. The same reasons as provided for the invention according to claim 1 of the main request apply *mutatis mutandis* for the invention according to claim 1 of auxiliary requests 1 to 20, which thus also fail to disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

I. Aperribay L. Bühler

Decision electronically authenticated