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Efficacy of FP-025

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Published in:

Allergy: European Journal of Allergy and Clinical Immunology

DOI:

[10.1111/all.15513](https://doi.org/10.1111/all.15513)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:

2023

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Ravanetti, L., Dekker, T., Guo, L., Dijkhuis, A., Dierdorp, B. S., Diamant, Z., Florquin, S., & Lutter, R. (2023). Efficacy of FP-025: A novel matrix metalloproteinase-12 (MMP-12) inhibitor in murine allergic asthma. *Allergy: European Journal of Allergy and Clinical Immunology*, 78(2), 559-562. <https://doi.org/10.1111/all.15513>

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Predicting probability of tolerating discrete amounts of peanut protein in allergic children using epitope-specific IgE antibody profiling

Maria Suprun | Paul Kearney | Clive Hayward | Heather Butler | Robert Getts | Scott H. Sicherer | Paul J. Turner
Dianne E. Campbell | Hugh A. Sampson



ARTICLE SUMMARY

- Existing diagnostic testing is not predictive of severity or the threshold dose of clinical reactivity, and many patients still require an Oral Food Challenge (OFC). While OFCs are very useful for making an allergy diagnosis and determining clinical reactivity, they often cause anaphylaxis, which can increase patient anxiety, and are time and resource intensive.¹
- An extensive validation was performed across 5 cohorts (all with confirmed oral food challenge results) across six different countries. Cohorts used: BOPI, OPIA, CAFETERIA, CoFAR6, and PEPITES with specimens from Australia, UK, US, Ireland, and Germany.
- This paper reports the first validated algorithm using two key peanut specific IgE epitopes to predict probabilities of reaction to different amounts of peanut in allergic subjects and may provide a useful clinical substitute for peanut oral food challenges.
- Using the algorithm, subjects were assigned into "high", "moderate", or "low" dose reactivity groups. On average, subjects in the "high" group were 4 times more likely to tolerate a specific dose, compared to the "low" group.¹ For example, 88% of patients in the high dose reactivity group were able to tolerate ≥ 144 mg of peanut protein whereas only 29% were able to tolerate the same amount in the low dose reactivity group.¹⁻²

CLINICAL CONSIDERATIONS

- The new epitope test offers more granular information to help clinicians stratify treatment and peanut avoidance plans for their patients.
- See below for summary of clinical considerations based on threshold reactivity level.¹

allergenis peanut diagnostic result	clinical considerations ¹
likely allergic – low dose reactor	<ul style="list-style-type: none">inform or avoid oral food challenge to reduce risk of anaphylaxisconfirm strict avoidance of peanutconsider immunotherapy to reduce risk of reaction
likely allergic – moderate dose reactor	<ul style="list-style-type: none">consider a single oral food challenge (30 to 100 mg) to reduce anxiety and improve quality of lifeless stringent avoidance of peanut regimeconsider inclusions of precautionary labeled foods such as 'May contain peanut'consider immunotherapy to reduce risk of reaction
likely allergic – high dose reactor	<ul style="list-style-type: none">consider a single oral food challenge (100 to 300 mg) to reduce anxiety and improve quality of lifeless stringent avoidance of peanut regimeconsider inclusions of precautionary labeled foods such as 'May contain peanut'consider starting immunotherapy at higher doses to shorten time to maintenance dose
unlikely allergic	<ul style="list-style-type: none">oral food challenge to rule out the diagnosis of peanut allergy

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REFERENCES

- Suprun M, Kearney P, Hayward C, et al. Predicting probability of tolerating discrete amounts of peanut protein in allergic children using epitope-specific IgE antibody profiling. *Allergy*. 2022;00:1-9. doi: 10.1111/all.15477
- Sindher SB, Long A, Chin AR, Hy A, Sampath V, Nadeau KC, Chinthrajah RS. Food allergy, mechanisms, diagnosis and treatment: Innovation through a multi-targeted approach. *Allergy*. 2022 Jun 22. doi: 10.1111/all.15418. Epub ahead of print. PMID: 35730331.

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LETTER

Efficacy of FP-025: A novel matrix metalloproteinase-12 (MMP-12) inhibitor in murine allergic asthma

To the Editor,

Asthma is a heterogeneous disease, as reflected by differences in age of onset, severity, treatment response and inflammatory profile. Matrix metalloprotease (MMP)-12 has been associated with inflammation in various subtypes of asthma.¹ In allergic asthma, MMP-12 activity has been implicated in the accumulation of neutrophils and eosinophils, in regulating macrophage functions and in the development of airway hyperresponsiveness (AHR).¹ To date, the underlying mechanisms by which MMP-12 may drive asthma pathophysiology have not been defined, nor has inhibition of MMP-12 as a targeted therapy for asthma been assessed in humans. FP-025 is a novel, potent, and highly selective non-hydroxamate inhibitor of MMP-12 with 90-fold selectivity over the closest family member (MMP-2) and two to three orders of magnitude over the seven other MMP family members. In an established mouse model of persistent house dust mite (HDM) allergic asthma,² we explored the effect of increasing doses (0–100 mg/kg, daily for 7 days) of oral FP-025 on airway pathophysiology, with Prednisone (5 mg/kg) given intraperitoneally as control treatment (Figure 1A).³ FP-025 did not induce behavioral or physical signs of discomfort nor differences in body weight compared with controls, even at the highest dose (Figure 1B). FP-025 100 mg/kg abrogated airway hyperresponsiveness (AHR) to a similar extent as Prednisone (Figure 1C). Similarly, the highest dose of FP-025 significantly reduced numbers of total bronchoalveolar lavage (BAL) cells, comparable to Prednisone (Figure 1D). Numbers of eosinophils, neutrophils, macrophages, inflammatory-migratory dendritic cells (DCs), B lymphocytes, CD4⁺ T lymphocytes, but not CD8⁺ T lymphocytes, were significantly reduced in BAL by 100 mg/kg FP-025, like with Prednisone (Figure 1E). Prednisone, however, also attenuated CD8⁺ T lymphocytes.

FP-025 reduced peri-bronchial and peri-arterial cellular infiltrates in lungs of HDM-sensitized mice in a dose-dependent manner, without affecting total inflammation scores. Furthermore, both the alpha-smooth muscle actin (α -SMA) stain, as a marker of fibrosis, and mucus production by PAS stain were reduced by 100 mg/kg FP-025 in lungs of HDM-sensitized mice (Figure 2A).

We found that the bronchial epithelial cells are the predominant source of MMP-12, and FP-025 highly reduced MMP-12 expression in lungs of HDM-sensitized mice, comparable to the stain for untreated mice (Figure 2B). Interestingly, and in line with total inflammation scores, in lung parenchyma, numbers of total inflammatory cells (Figure 2C), eosinophils, neutrophils, macrophages, inflammatory-migratory (CD11b⁺) dendritic cells (DCs), CD4⁺ lymphocytes, CD8⁺ lymphocytes and B lymphocytes were not affected (Figure 2D). Additionally, none of the mediators of innate, Th1- and Th2-responses, chemoattractant chemokines and growth factors (Figure 2E) were affected by FP-025. Importantly, FP-025 efficiently reduced levels of MMP-12 in BAL and lung parenchyma of HDM-sensitized mice in a dose-dependent manner (Figure 2F).

Respiratory viruses are the most frequent trigger of asthma exacerbations.⁴ As MMP-12 has a dualistic modulatory effect on the interferon (IFN)- α -mediated anti-viral response,⁵ we evaluated the efficacy of the anti-viral immune response to influenza upon FP-025 treatment (Figure S1A). No differences in AHR and IFN- α (below lower limit of detection) levels were noted between FP-025-treated and untreated mice, but FP-025 markedly reduced body weight loss and viral load (Figure S1B,C). Furthermore, FP-025 significantly reduced T lymphocyte numbers in lung parenchyma of infected mice, whereas myeloid cell numbers as well as that of lymphoid and myeloid BAL cells were unaffected. In parallel, FP-025 reduced BALF levels of IL-12 and CCL5 (Figure S1D–F). Also, in infected mice, FP-025 significantly reduced levels of MMP-12 in BAL and lung parenchyma (Figure S2).

In all, FP-025 in a dose-dependent manner significantly attenuated AHR, BAL inflammatory cell numbers and lung pathophysiology in a mouse model of persistent HDM-allergic asthma. FP-025 markedly reduced MMP-12 expression in airway epithelial cells and levels of MMP-12 in lung parenchyma and airways, indicating that the enhanced expression in allergic asthma depends on an auto-crine process. FP-025 did not negatively affect anti-viral responses, contributing to its safety profile. These findings warrant interventions with FP-025 in allergic asthma, also as FP-025 showed safety,

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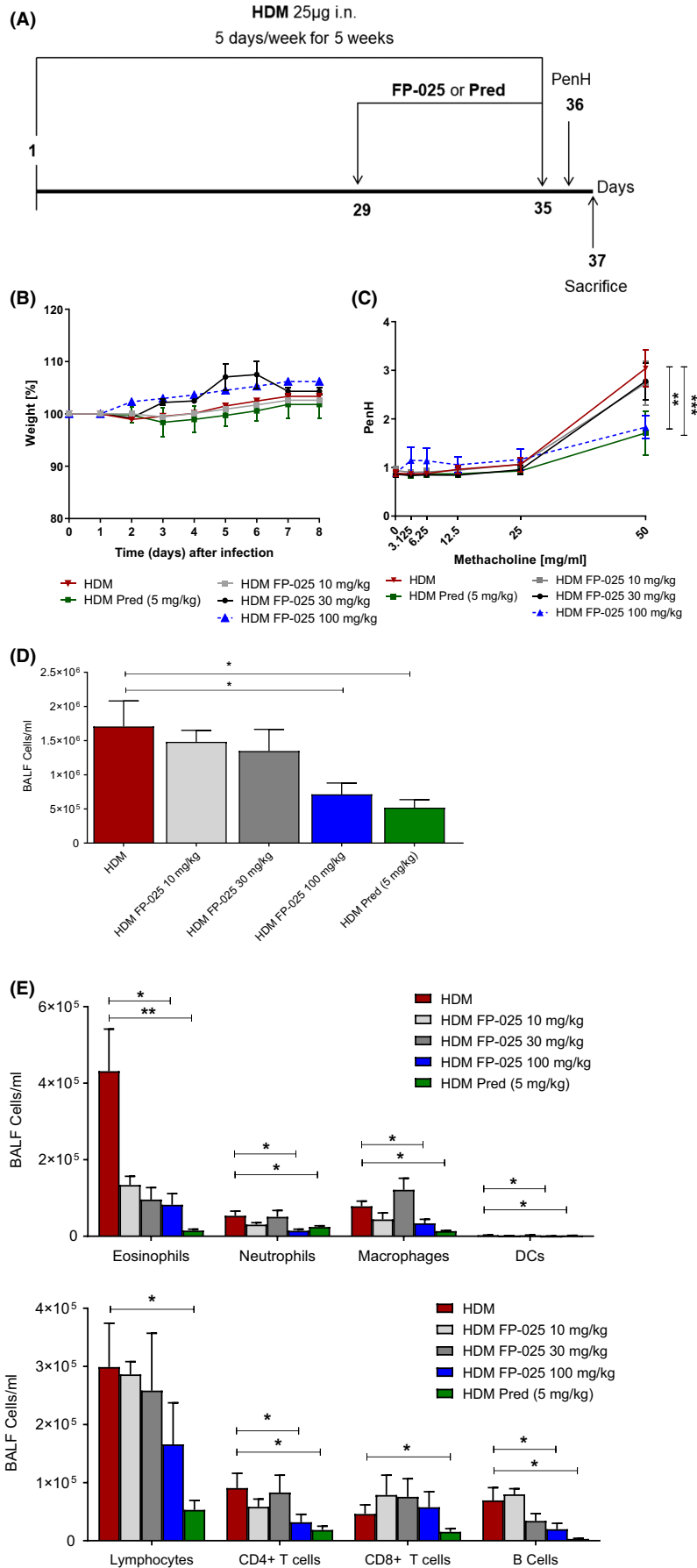


FIGURE 1 FP-025 significantly suppressed allergic asthma features. (A) Experimental outline (Appendix S1). (B) The body weight assessed daily during FP-025 treatment. (C) Analysis of the AHR on day 36 of the sensitization schedule by Penh. (D) Total cell counts, (E) differential immune cell count in BAL. Data are representative of two independent experiments with four mice per group. (C) Data represent mean \pm SEM (two-way ANOVA followed by Bonferroni's post-test); * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for the comparison between indicated groups. (D, E) Data represent mean \pm SEM (t-test); * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for the comparison between indicated groups.

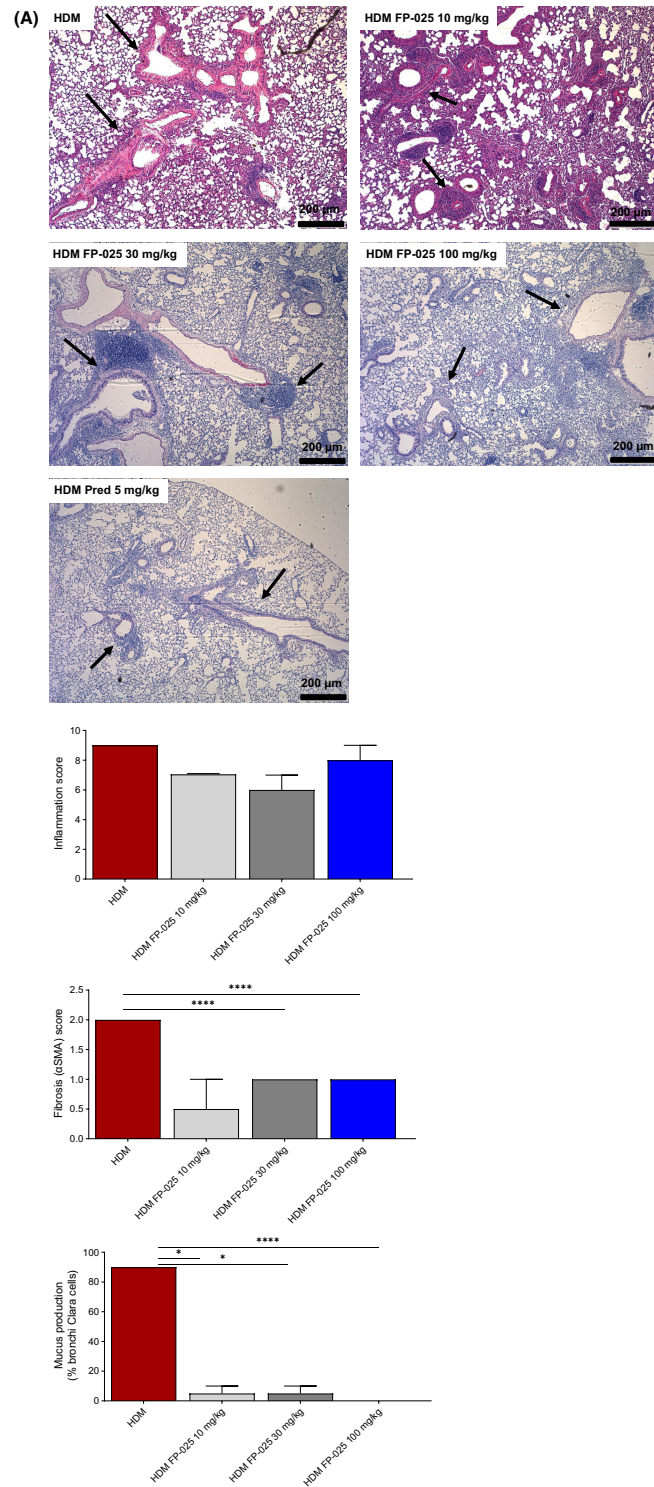


FIGURE 2 FP-025 attenuated fibrosis and mucus production but did not affect immune cell numbers and humoral factor levels in lung parenchyma in HDM-sensitized mice. C57BL/6J mice were sensitized (i.n.) with HDM and treated or not with increasing doses of FP-025 or systemic prednisone (Pred) for 7 days. (A) Representative H&E stains, scores for inflammation, fibrosis (α -SMA) and mucus production (assessed by a blinded expert pathologist [SF]); (B) MMP-12 stain (5 \times magnification) of perfused lungs from the five groups. Arrows indicate inflammatory infiltrate (A) and MMP-12 localization (B). (C) Total cell counts, (D) Differential immune cell count in lung parenchyma. (E) Levels of cytokines, chemokines and growth factors in lung homogenate. IFN- α was below level of detection. (F) MMP-12 levels in BAL and lung homogenate. Data are representative of two independent experiments with four mice per group. Data represent mean \pm SEM (t-test); * p < 0.05, for the comparison between indicated groups.

(B)

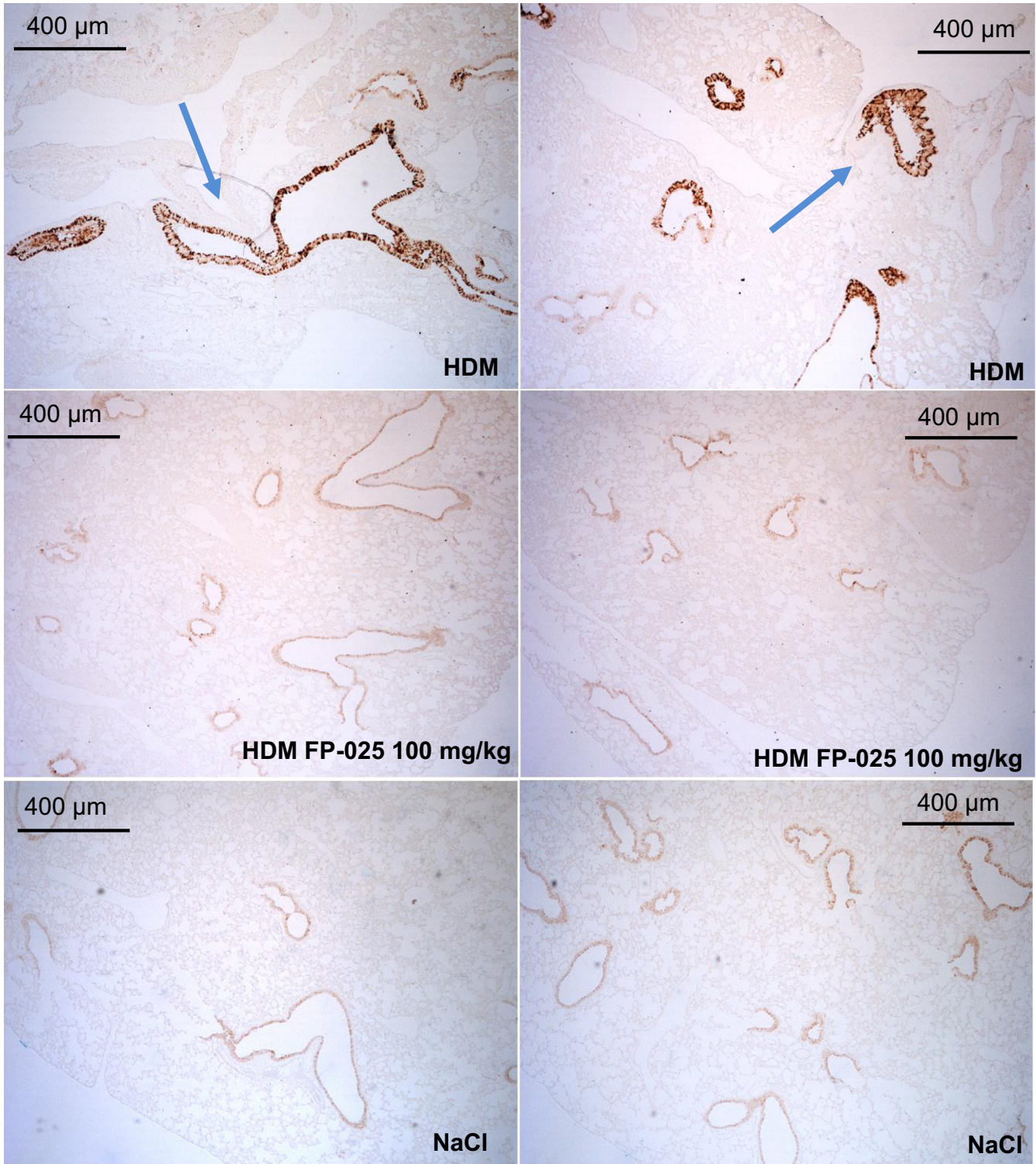


FIGURE 2 (Continued)

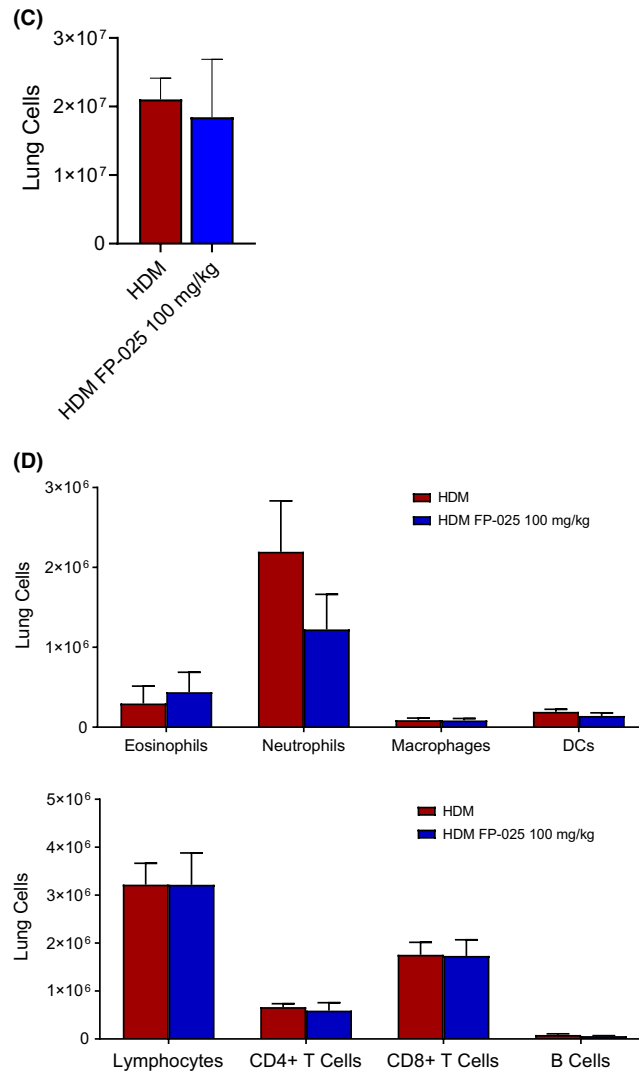


FIGURE 2 (Continued)

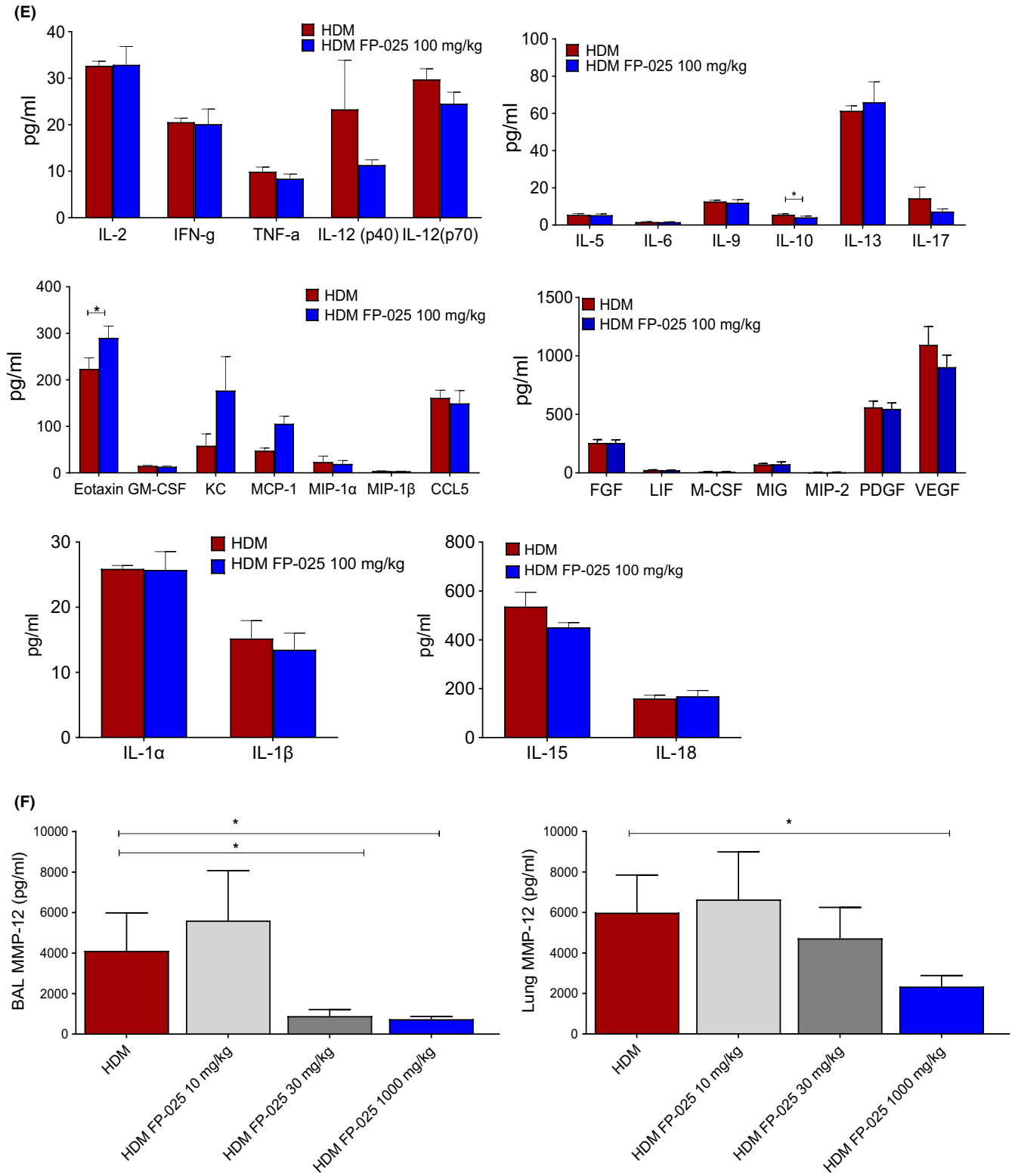


FIGURE 2 (Continued)

tolerability, and good pharmacokinetics characteristic in a randomized, placebo-controlled, single, and multiple ascending dose study in healthy subjects.⁶

ACKNOWLEDGMENTS

We thank David Lau, Wenjin Yang, and Ben Chien (all Foresee Pharmaceuticals Co., Ltd) for sharing their knowledge and expertise on FP-025. This study was financially supported by Foresee Pharmaceuticals Co., Ltd.

FUNDING INFORMATION

Foresee Pharmaceuticals Co., Ltd

CONFLICT OF INTEREST

L.R. receives funding from Foresee Pharmaceuticals, Chiesi Farmaceutici. Z.D. has received honoraria for serving on advisory boards or as a consultant with ALK, AstraZeneca, Boehringer-Ingelheim, GSK, HAL-Allergy, MSD, Sanofi-Genzyme. She acted as Research Director at QPS-NL: this institution has received research support from Foresee Pharmaceuticals, Novartis and Patara pharma. R.L. receives funding from Foresee Pharmaceuticals, Chiesi Farmaceutici, Astra Zeneca, MedImmune, GSK. The rest of the authors declare that they have no relevant conflicts of interest.

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REFERENCES

1. Abd-Elaziz K, Jesenak M, Vasakova M, Diamant Z. Revisiting matrix metalloproteinase 12: its role in pathophysiology of asthma and related pulmonary diseases. *Curr Opin Pulm Med*. 2021;27(1):54-60.
2. Johnson JR, Wiley RE, Fattouh R, et al. Continuous exposure to house dust mite elicits chronic airway inflammation and structural remodeling. *Am J Respir Crit Care Med*. 2004;169(3):378-385.
3. Ravanetti L, Dijkhuis A, Dekker T, et al. IL-33 drives influenza-induced asthma exacerbations by halting innate and adaptive antiviral immunity. *J Allergy Clin Immunol*. 2019;143(4):1355-1370 e1316.
4. Ravanetti L, Dijkhuis A, Sabogal Pineros YS, et al. An early innate response underlies severe influenza-induced exacerbations of asthma in a novel steroid-insensitive and anti-IL-5-responsive mouse model. *Allergy*. 2017;72(5):737-753.
5. Marchant DJ, Bellac CL, Moraes TJ, et al. A new transcriptional role for matrix metalloproteinase-12 in antiviral immunity. *Nat Med*. 2014;20(5):493-502.
6. Abd-Elaziz K, Voors-Pette C, Wang KL, et al. First-in-man safety, tolerability, and pharmacokinetics of a novel and highly selective inhibitor of matrix Metalloproteinase-12, FP-025: results from two randomized studies in healthy subjects. *Clin Drug Investig*. 2021;41(1):65-76.

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