Safe administration of subsequent mRNA COVID-19 vaccine doses following a possible allergic reaction to the first dose

The mRNA COVID-19 vaccines are highly effective in preventing severe COVID-19. After the first vaccination dose, allergic reactions are reported in up to 2.2%, while severe anaphylaxis is very rare (estimated <1/100 000). IgE-mediated allergy to polyethylene glycol (PEG), non-IgE-mediated PEG-reactions, and direct lipid nanoparticle (LNP)-mediated mast cell activation have been proposed as immune mechanisms causing anaphylactoid reactions. Severe allergic reactions to the first dose of an mRNA vaccine are considered a relative contraindication for a subsequent mRNA COVID-19 vaccine dose (i.e. 0.5 mL; 100 μg mRNA) given 30 min apart and followed by a 1-h observation. Considering that the five-step graded protocol may also result in tolerance induction, the five-step graded protocol was used in patients with more severe reactions and a positive skin test. In contrast, patients with milder reactions and negative skin tests were vaccinated using the two-step graded protocol. All subjects received prophylactic treatment with a standard dose of an H1-antihistamine once daily for 6 days, starting 3 days before the vaccination. We opted to initiate the prophylactic antihistamine already 3 days before the vaccination – instead of a single dose before the vaccination – given that urticaria is often insufficiently suppressed by a single dose. None of the 17 patients experienced severe allergic symptoms during observation and follow-up. Three subjects developed very mild symptoms with spontaneous improvement (Table 1). Over the next months, 13 of 17 patients also received a booster vaccination (Table 2). The four subjects who had received the second dose with the five-step protocol were booster vaccinated with the two-step graded protocol. The remaining nine subjects received the booster as an unfractionated vaccination. All but one patient received antihistamines. Fractionated and unfractionated booster vaccinations were tolerated well in all these patients (Table 2). Within the four patients not booster vaccinated during our follow-up period, one patient had COVID-19 infection before he was able to get the booster and three patients decided against the booster.

In conclusion, we found that antihistamine premedication and graded immunization protocols allowed a safe administration of the mRNA COVID-19 vaccine in patients with a possible allergic reaction to the first dose. None of our patients showed apparent signs of an immediate-type allergy after the second or the booster vaccination. In contrast, others reported mild anaphylactic symptoms in 26–38% of subjects receiving the second dose of Pfizer/BioNTech with antihistamine premedication or graded dosing.

We administered the second dose of the mRNA-1273 vaccine using either a five-step or a two-step graded protocol, that is, 1%-10%-20%-30%-40% or 10%-90% of the total mRNA-1273 vaccine dose (i.e. 0.5 mL; 100 μg mRNA) given 30 min apart and followed by a 1-h observation. Considering that the five-step graded protocol may not be necessary for further vaccinations in patients with mild reactions to the first dose of mRNA vaccine.
| No. | Age (y), sex | Allergy history | 1st mRNA vaccination | Time to reaction | Symptoms | ANA grade (Ring and Messmer) | Therapy of ANA | Diagnostics | Intradermal test | Within 24 h | 2nd mRNA vaccination | Vaccination protocol | Outcome |
|-----|-------------|-----------------|----------------------|------------------|----------|-----------------------------|----------------|-------------|------------------|------------|---------------------|---------------------|---------|
| 1   | 47, f       | CSU, DA         | mRNA-1273            | 5 min / 30 h     | Dizziness, tachycardia, urticaria // dyspnoea and angio-oedema | II°          | A-H, GC       | 5-step administration of mRNA-1273 | + (x)      | mRNA-1273          | No allergic symptoms |
| 2   | 42, f       | mRNA-1273      | 1 h                  | 30 h             | Urticaria | I°                         | A-H           | ND          | No allergic symptoms |
| 3   | 30, m       | mRNA-1273      | 10 min               | Urticaria, dizziness, oral swelling | II°          | A-H, GC       | No allergic symptoms |
| 4   | 43, f       | U, A, DA, BA    | mRNA-1273            | 2 min            | Angio-oedema | I°                        | A-H           | + (c)       | No allergic symptoms |
| 5   | 26, f       | DA, FA          | mRNA-1273            | 5 min / 6 h      | Flush, pruritus | I°                         | A-H + (a)     | ND         | No allergic symptoms |
| 6   | 55, f       | mRNA-1273      | 15 min               | Fatigue // rash, pruritus, dyspnoea | II°          | A-H, GC       | No allergic symptoms |
| 7   | 43, f       | CSU, PEG-allergy | BNT 162B2           | 1 h              | Rhinitis, tongue burning (wanishing for 2 day) | I°             | NP (a) | 2-step administration of mRNA-1273 | Lip numbness, (h) |
| 8   | 55, f       | ARC, DA         | mRNA-1273            | 20 min           | Headache, pruritus, angio-oedema | I°             | ND       | No allergic symptoms |
| 9   | 50, f       | DA, BA          | mRNA-1273            | 1 min / 1 h      | Nausea, sore throat // urticaria, angio-oedema | II°          | No allergic symptoms |
| 10  | 66, f       | mRNA-1273      | 5 min                | Angio-oedema, pruritus | I°             | ND       | No allergic symptoms |
| 11  | 32, f       | ARC             | mRNA-1273            | 5 min / 24 h     | Fatigue, dizziness / urticaria, dyspnoea | I-II°         | A-H, BD, OCS | No allergic symptoms |
| 12  | 20, m       | ARC, BA         | mRNA-1273            | 4 h              | Dyspnoea (wanishing for 6 day) | II° / # BO | IR       | No allergic symptoms |
| 13  | 56, f       | mRNA-1273      | 2 h                  | Headache, flush | I°             | A-H           | IR         | No allergic symptoms |
| 14  | 53, f       | mRNA-1273      | 4 h                  | Angio-oedema | I°             | No allergic symptoms |
| 15  | 37, f       | ARC             | mRNA-1273            | 30 min           | Angio-oedema | I°             | IR         | No allergic symptoms |
### Table 1
Continued

| No. | Age (y), sex | Allergy history | 1st mRNA vaccination | Diagnostics | 2nd mRNA vaccination |
|-----|--------------|-----------------|----------------------|-------------|----------------------|
|     |              |                 | 1st mRNA vaccination |             |                      |
|     |              |                 | Vaccine type         |             |                      |
|     |              |                 | Time to reaction     |             |                      |
|     |              |                 | Symptoms             |             |                      |
|     |              |                 | ANA grade            |             |                      |
|     |              |                 | (Ring and Messmer)   |             |                      |
|     |              |                 | Therapy of ANA       |             |                      |
|     |              |                 | Skin prick test      |             |                      |
|     |              |                 | Macrogol 400         |             |                      |
|     |              |                 | Macrogol 6000        |             |                      |
|     |              |                 | Macrogol 1273        |             |                      |
|     |              |                 | Polysorbate 80       |             |                      |
|     |              |                 | TRIS                 |             |                      |
|     |              |                 | mRNA-1273            |             |                      |
|     |              |                 | Time to reaction     |             |                      |
|     |              |                 | Symptoms             |             |                      |
|     |              |                 | ANA grade            |             |                      |
|     |              |                 | (Ring and Messmer)   |             |                      |
|     |              |                 | Therapy of ANA       |             |                      |
|     |              |                 | Skin prick test      |             |                      |
|     |              |                 | Macrogol 400         |             |                      |
|     |              |                 | Macrogol 6000        |             |                      |
|     |              |                 | Macrogol 1273        |             |                      |
|     |              |                 | Polysorbate 80       |             |                      |
|     |              |                 | TRIS                 |             |                      |
|     |              |                 | mRNA-1273            |             |                      |

| No. | Age (y), sex | Allergy history | 1st mRNA vaccination | Diagnostics | 2nd mRNA vaccination |
|-----|--------------|-----------------|----------------------|-------------|----------------------|
| 16  | 58, m        | ARC, BA         | BNT 162B2            | 10 h        | Sore throat, hoarseness, angio-oedema, pruritus, asthma |
|     |              |                 | Macrogol 400         |             | AH, GC |
|     |              |                 | Macrogol 6000        |             | - |
|     |              |                 | Polysorbate 80       |             | - |
|     |              |                 | TRIS                 |             | - |
|     |              |                 | mRNA-1273            |             | - |
|     |              |                 | Time to reaction     |             | - |
|     |              |                 | Symptoms             |             | - |
|     |              |                 | ANA grade            |             | - |
|     |              |                 | (Ring and Messmer)   |             | - |
|     |              |                 | Therapy of ANA       |             | - |
|     |              |                 | Skin prick test      |             | - |
|     |              |                 | Macrogol 400         |             | - |
|     |              |                 | Macrogol 6000        |             | - |
|     |              |                 | Macrogol 1273        |             | - |
|     |              |                 | Polysorbate 80       |             | - |
|     |              |                 | TRIS                 |             | - |
|     |              |                 | mRNA-1273            |             | - |
| 17  | 42, f        | ARC, BA, BA     | mRNA-1273            | 5 min       | Dizziness |
|     |              |                 | Macrogol 400         |             | - |
|     |              |                 | Macrogol 6000        |             | - |
|     |              |                 | Polysorbate 80       |             | - |
|     |              |                 | TRIS                 |             | - |
|     |              |                 | mRNA-1273            |             | - |

Grading of possible allergic reaction: §, patient 17 presented with dizziness only. Differential diagnosis includes a vasovagal reaction. #, patient 12 suffered from dyspnoea. Differential diagnosis includes uncontrolled asthma. Specifications to test results and reactions: (a) positive after 30–45 min; (b) positive after 6–24 h; (c) positive skin reaction and urticaria; (d) positive after 10 h; (e) not performed due to CSU and daily antihistamine therapy; (f) positive after 4 min; (g) positive after 60 min; (h) spontaneous improvement without therapy. A, angio-oedema; ANA, anaphylaxis; AH, antihistamine; ARC, allergic rhinoconjunctivitis; BA, bronchial asthma; BD, bronchodilator; CSU, chronic spontaneous urticaria; d, day(s); DA, drug allergy; FA, food allergy; f, female; GC, glucocorticoid, h, hour(s); ICS, inhaled corticosteroids; IR, irritative skin reaction; m, male; min, minutes; ND, not determined; NP, not performed; TRIS, trometamol/tromethamine; U, urticaria; +, skin prick testing defined as positive: weal >3 mm. // indicates a two-phase reaction.

### Table 2
Follow-up and outcome of booster administration with mRNA COVID-19 vaccine

| No. | Age (y), sex | Vaccine type | Booster vaccination | Late onset symptoms (>24 h) |
|-----|--------------|--------------|---------------------|----------------------------|
|     |              | mRNA-1273    | 2-step administration | Ear redness after 1st dose |
| 1   | 47, f        | mRNA-1273    | Yes                 | Urticaria 24 h after vaccination |
| 2   | 42, f        | mRNA-1273    | Yes                 | No allergic symptoms |
| 3   | 30, m        | No booster vaccination | - | |
| 4   | 43, f        | mRNA-1273    | Yes                 | Pruritus after 1st dose* |
| 5   | 26, f        | No booster vaccination | - | |
| 6   | 56, f        | mRNA-1273    | 2-step Administration | No allergic symptoms |
| 7   | 43, f        | mRNA-1273    | Unfractionated      | No allergic symptoms |
| 8   | 56, f        | mRNA-1273    | Unfractionated      | No allergic symptoms |
| 9   | 50, f        | mRNA-1273    | Unfractionated      | Tongue burning* |
| 10  | 60, f        | mRNA-1273    | Unfractionated      | Burning sensation of the skin, swallowing problems* |
| 11  | 32, f        | No booster vaccination | - | |
| 12  | 20, m        | mRNA-1273    | Unfractionated      | No allergic symptoms |
| 13  | 56, f        | mRNA-1273    | Yes                 | No allergic symptoms |
| 14  | 53, f        | BNT 162B2    | Unfractionated      | No allergic symptoms |
| 15  | 37, f        | mRNA-1273    | Yes                 | No allergic symptoms |
| 16  | 58, m        | No booster vaccination | - | |
| 17  | 42, f        | mRNA-1273    | Unfractionated      | No allergic symptoms |

Abbreviations and specification: f, female; d, day(s); h, hour(s); m, male; *spontaneous improvement without therapy.
The limitations of our study include the small number of patients, absence of a control group and mainly mild reactions to the first dose. Also, the skin tests were not formally validated in healthy subjects without reactions. Unspecific positive skin tests can thus not be excluded. Nevertheless, we believe that our approach decreased hesitancy to get further vaccinations in subjects with possible allergic reactions and enabled us to complete immunization schedules, including the booster dose.

Further studies are needed to define the benefit of graded protocols as well as the effect of premedication with antihistamines in patients with a history of possible allergic reactions to mRNA COVID-19 vaccines.

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Conflicts of interests
The authors declare no conflicts of interest.

Data availability statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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