

| Surface Marker | Clone | Fluorochrome | Company | Cat-Nr. | Panel |
|---------------------|--------|-----------------|-----------|-------------|---------|
| CD3 | UCHT1 | FITC | BioLegend | 300440 | 1, 2, 4 |
| CD4 | RPAT4 | APC Fire 750 | BioLegend | 300560 | 1 |
| CD25 | M-A251 | BV785 | BioLegend | 356140 | 1 |
| CD127 | A019D5 | APC | BioLegend | 351316 | 1 |
| CXCR5 | J25204 | PE/Dazzle 594 | BioLegend | 356928 | 1 |
| CD45RA | H100 | BV605 | BioLegend | 304134 | 1,2 |
| CCR7 | G043H7 | PerCP/Cy5.5 | BioLegend | 353220 | 1,2 |
| CCR6 | 11A9 | PE | BD | 559562 | 1 |
| CXCR3 | G025H7 | BV650 | BioLegend | 353730 | 1 |
| CCR4 | L2A1H4 | BV421 | BioLegend | 359414 | 1 |
| CD8 | SK1 | APC Fire 750 | BioLegend | 344746 | 2 |
| CD161 | HP3G10 | PE | BioLegend | 339904 | 2 |
| V87.2 | 3C10 | BV785 | BioLegend | 351722 | 2 |
| TCR γ/δ | 11F2 | APC | Miltenyi | 130-113-500 | 2 |
| V82 | B6 | BV421 | BioLegend | 331428 | 2 |
| CD19 | H1B19 | FITC | BioLegend | 302206 | 3, 4 |
| IgD | 1A6-2 | PE/Dazzle 594 | BioLegend | 348240 | 3 |
| CD45 | H130 | Alexa Fluor 700 | BioLegend | 304024 | 3, 4 |
| CD27 | 323 | BV421 | BioLegend | 302824 | 3 |
| CD38 | HIT2 | APC | BioLegend | 303510 | 3 |
| CD34 | 563 | PE | BD | 550761 | 3 |
| CD11c | B-LY6 | APC | BD | 559877 | 4 |
| CD14 | HCD14 | PE/Dazzle 594 | BioLegend | 325634 | 4 |
| CD16 | 3G8 | APC Fire 750 | BioLegend | 302060 | 4 |
| CD56 | HCD56 | PerCP/Cy5.5 | BioLegend | 318322 | 4 |
| CD11b | ICRF44 | PE | BioLegend | 301306 | 4 |
| CD123 | 6H6 | BV605 | BioLegend | 306026 | 4 |
| HLA-DR | L243 | BV785 | BioLegend | 307642 | 4 |

Supplementary Table S1: List of antibodies used for in-depth immunophenotyping.

| Panel 1 - CD4 T cells | | | |
|-------------------------------------|--------------------------------------|---|---|
| Cell type | Gating strategy | | |
| CD4+ T cells | CD3 ⁺ CD4 ⁺ | CXCR5 ⁺ | |
| T follicular helper (Tfh) | | CXCR5 ⁻ CD25 ^{high} CD127 ^{low} | |
| T regulatory cells (Tregs) | | CXCR5 ⁻ CD127 ⁺ CD25 ^{-/low} CXCR3 ⁺ CCR6 ⁻ | |
| T helper 1 (Th1) | | CXCR5 ⁻ CD127 ⁺ CD25 ^{-/low} CXCR3 ⁺ CCR6 ⁺ | |
| T helper 1/T helper 17 (Th1/Th17) | | CXCR5 ⁻ CD127 ⁺ CD25 ^{-/low} CXCR3 ⁻ CCR6 ⁻ CCR4 ⁺ | |
| T helper 17 (Th17) | | CXCR5 ⁻ CD127 ⁺ CD25 ^{-/low} CXCR3 ⁻ CCR6 ⁻ CCR4 ⁻ | |
| T helper 2 (Th2) | | CXCR5 ⁻ CD127 ⁺ CD25 ^{-/low} CXCR3 ⁻ CCR6 ⁻ CCR4 ⁻ | |
| T CD4 terminal effector (T CD4 TE) | | CCR7 ⁻ CD45RA ^{low} | |
| T CD4 Naïve | | CXCR5 ⁻ CD127 ⁺ CD25 ^{-/low} CXCR3 ⁻ CCR6 ⁻ CCR4 ⁻ CCR7 ⁺ CD45RA ^{high} | |
| Panel 2 - CD8, γ/δ and MAIT T cells | | | |
| Cell type | Gating strategy | | |
| CD8+ T cells | CD3 ⁺ | TCR γ/δ ⁻ | CD16 ^{high} NOT Vα7.2 ⁺ |
| γ/δ Vd2 ⁺ (T gd Vd2+) | | TCR γ/δ ⁺ | Vd2 ⁺ |
| γ/δ Vd2 ⁻ (T gd non-Vd2) | | | Vd2 ⁻ |
| MAIT | | TCR γ/δ ⁻ Vd2 ⁻ | Vα7.2 ⁺ CD161 ^{high} |
| T CD8 Naïve | | CD8 ⁺ TCR γ/δ ⁻ Vd2 ⁻ | CCR7 ⁺ CD45RA ⁺ |
| T CD8 central memory (CM) | | | CCR7 ⁺ CD45RA ⁻ |
| T CD8 effector memory (EM) | | | CCR7 ⁻ CD45RA ⁻ |
| T CD8 terminal effector (TE) | | | CCR7 ⁻ CD45RA ⁺ |
| PANEL 3 - B cells and Progenitors | | | |
| Cell type | Gating strategy | | |
| Progenitors | CD45 ⁺ | CD34 ⁺ CD45 ^{low} | |
| Total B cells (B cells) | | CD19 ⁺ CD34 ⁻ | CD27 ⁻ IgD ⁺ |
| Naïve B cells (B naïve) | | | CD27 ⁺ IgD ⁺ |
| Nonswitched memory B cells (B NSM) | | | |
| Exhausted B cells (B EX) | | | CD27 ⁻ IgD ⁻ |

| Switched memory B cells (B SM) | | | CD27 ⁺ IgD ⁻ CD38 ^{low} |
|--|--|-------------------------------------|--|
| Plasmablasts | | | CD27 ⁺ IgD ⁻ CD38 ^{high} |
| Panel 4 - Monocytes, DCs, NK cells, Low-density basophils | | | |
| Cell type | Gating strategy | | |
| NK cells | CD45 ⁺ CD3 ⁻ CD19 ⁻ | | CD16 ^{+/-} CD56 ^{+/low} CD14 ⁻ CD11c ⁻ |
| Classic monocytes (C) | | | CD14 ⁺ CD16 ⁻ |
| Intermediate monocytes (I) | | CD11c ⁺ | CD14 ⁺ CD16 ⁺ |
| Nonclassic monocytes (NC) | | | CD14 ^{low} CD16 ⁺ |
| Myeloid dendritic cells (mDCs) | | CD16 ⁻ CD56 ⁻ | HLA-DR ⁺ CD11c ⁺ CD123 ^{low} |
| Plasmacytoid dendritic cells (pDCs) | | | HLA-DR ⁺ CD11c ⁻ CD123 ⁺ |
| Low-density basophils (LD) | | | HLA-DR ⁻ CD123 ⁺ CD11b ⁺ |

Supplementary Table S2: Gating strategies for in-depth immuno-phenotyping of immune cell subsets.

| Characteristics | PA+BA+placebo (n=24) | 2FL+placebo (n=24) | 2FL+PA+BA (n=24) |
|----------------------------|-------------------------|-----------------------|---------------------|
| Female sex | 13 (54.2%) | 9 (37.5%) | 13 (54.2%) |
| Age, years | 62(±9) | 67 (±12) | 65 (±8) |
| Duration of disease, years | 7 (±7) | 6 (±6) | 4 (±4) |
| BMI | 26 (±4) | 26 (±3) | 25 (±3) |
| Subgroups | | | |
| akinetetic-rigid | 8 (33.3%) | 9 (37.5%) | 11 (45.8%) |
| equivalent | 14 (58.3%) | 12 (50%) | 12 (50%) |
| tremordominant | 2 (8.3 %) | 3 (12.5%) | 1 (4.17%) |
| Medication | | | |
| LEDD [mg] | 770 (±302) | 785 (±267) | 756 (±261) |
| 95% CI | 642.1-897.1 | 672.2-897.3 | 646-866.5 |
| Benserazide | 24 (100%) | 22 (91.7%) | 23 (95.8%) |
| Carbidopa | 4 (16.7%) | 5 (20.8%) | 2 (8.3%) |
| Piribedil | 2 (8.3%) | 0 | 2 (8.3%) |
| Rotigotine | 2 (8.3%) | 3 (12.5%) | 3 (12.5%) |
| Ropinirole | 2 (8.3%) | 1 (4.17%) | 2 (8.3%) |
| Pramipexole | 4 (16.7%) | 2 (8.3%) | 4 (16.7%) |
| Rasagiline | 13 (54.2%) | 8 (33.3%) | 14 (58.3%) |
| Selegiline | 3 (12.5%) | 9 (37.5%) | 3 (12.5%) |
| Safinamide | 2 (8.3%) | 1 (4.2%) | 2 (8.3%) |
| COMT-inhibitor | 6 (25%) | 8 (33.3%) | 9 (37.5%) |
| Amantadine | 2 (8.3 %) | 2 (8.3 %) | 1 (4.2%) |
| Apomorphine | 0 | 0 | 0 |
| Anticholinergics | 0 | 1 (4.2%) | 0 |
| Clozapine | 1 (4.2%) | 0 | 2 (8.3%) |
| Quetiapine | 1 (4.2%) | 3 (12.5%) | 1 (4.2%) |
| PD Clinical Scores | | | |
| MDS-UPDRS I | 10 (±10) | 17 (±12) | 17 (±13) |
| 95% CI | 12.6-21 | 12.1-22.5 | 11.2-22.1 |
| MDS-UPDRS II | 9 (±6) | 9 (±8) | 10 (±9) |

| | | | |
|--------------------|-----------------|-----------------|-----------------|
| 95% CI | 6.8-12.1 | 6.3-12.7 | 6-13.4 |
| MDS-UPDRS III | 29 (± 17) | 33 (± 16) | 30 (± 16) |
| 95% CI | 22.1-36.3 | 26.3-40 | 23-36.8 |
| MDS-UPDRS IV | 3 (± 3) | 5 (± 5) | 3 (± 3) |
| 95% CI | 1.8-4.2 | 2.5-6.3 | 1.4-4.1 |
| Hoehn & Yahr scale | 2 (± 1) | 2 (± 1) | 2 (± 1) |
| 95% CI | 1.9-2.5 | 1.9-2.4 | 1.9-2.7 |
| PANDA | 25 (± 4) | 33 (± 16) | 30 (± 16) |
| 95% CI | 23.7-26.7 | 18.9-24.8 | 20.8-26.1 |
| Olfactory score | 8 (± 3) | 7 (± 3) | 7 (± 3) |
| 95% CI | 6.8-9 | 5.9-8.1 | 5.6-8.1 |

Supplementary Table 3. Demographic data and characteristics of patients prior to therapeutic intervention. Main demographics and clinical and treatment characteristics of participants at study entry. Data are presented as the mean \pm SD or n (%).

| Adverse Event (AE) | Therapeutic Intervention | CTCAE Grade 1 (Mild) | CTCAE Grade 2 (Moderate) | CTCAE Grade 3 (Severe) | CTCAE Grade 4 (Life-threatening) |
|--|---------------------------------|-----------------------------|---------------------------------|-------------------------------|---|
| Flatulence / Bloating | PA+BA | 3/24 | — | — | — |
| | 2FL | 5/23 | — | — | — |
| | PA+BA+2FL | 4/24 | — | — | — |
| Diarrhea | PA+BA | 2/24 | — | — | — |
| | 2FL | 2/23 | — | — | — |
| | PA+BA+2FL | 4/24 | — | — | — |
| Abdominal pain / cramps | PA+BA | 0/24 | — | — | — |
| | 2FL | 1/23 | — | — | — |
| | PA+BA+2FL | 0/24 | — | — | — |
| Nausea | PA+BA | 1/24 | — | — | — |
| | 2FL | 2/23 | — | — | — |
| | PA+BA+2FL | 0/24 | — | — | — |
| Headache | PA+BA | — | — | — | — |
| | 2FL | — | — | — | — |
| | PA+BA+2FL | — | — | — | — |
| Systemic reactions (allergy, intolerance) | PA+BA | — | — | — | — |
| | 2FL | — | — | — | — |
| | PA+BA+2FL | — | — | — | — |

Supplementary Table 4. Adverse Effects and Severity Grading: Frequency and severity of adverse events (AEs) observed during the 6-month intervention study. Severity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0), with Grade 1 indicating mild symptoms requiring no intervention, Grade 2 indicating moderate symptoms requiring medical intervention, Grade 3 indicating severe symptoms requiring hospitalization or therapy, and Grade 4 indicating life-threatening events. The numbers in the columns represent the number of participants per group who experienced each event at the specified severity, out of a total of 24 (23 for the 2FL group) participants per group.

| Dietary change in the last 6 months | Baseline | Visit 1 (3 months) | Visit 2 (6 months) |
|--|-----------------|---------------------------|---------------------------|
| PA+BA+placebo | 0/24 | 0/24 | 0/24 |
| 2FL+placebo | 0/24 | 1/23 | 1/23 |
| 2FL+PA+BA | 0/24 | 2/24 | 2/24 |

Supplementary Table S5. Dietary change in the last 6 months: This table indicates the number of participants who reported changes in their diet during the last 6 months. Dietary intake was assessed at baseline (month 0), after 3 months (V1, visit 1), and after 6 months (V2, visit 2) using a standardized dietary questionnaire. Values represent the number of participants per intervention group reporting dietary changes and the total number of participants in each group (n = 24).