ADDITIONAL INFORMATION

Real-world effectiveness of early intervention with fixed-dose tiotropium/olodaterol vs tiotropium in Japanese patients with COPD: a high-dimensional propensity score–matched cohort analysis

Shigeo Muro, Masaru Suzuki, Shuhei Nakamura, Jocelyn Ruoyi Wang, Elizabeth M. Garry, Wataru Sakamoto, Sabrina de Souza

1Department of Respiratory Medicine, Nara Medical University, Kashihara, Nara, Japan; 2Department of Respiratory Medicine, Faculty of Medicine, Hokkaido University, Sapporo, Japan; 3Nippon Boehringer Ingelheim Co., Ltd., Tokyo, Japan; 4Science, Aetion Inc., Boston, MA, USA; 5Boehringer Ingelheim International GmbH, Ingelheim, Germany

Additional Table S1a Patient selection in the primary and sensitivity analysis cohorts
Additional Table S1b Patient selection in the sensitivity analysis cohorts for the post hoc extension study period (from 28 September 2015 to 31 March 2020)
Additional Table S2 Sensitivity analyses for escalation to triple therapy (fixed-dose or concurrent ICS/LAMA/LABA) during the prespecified study period (from 28 September 2015 to 31 March 2019)
Additional Fig. S1 Sensitivity analyses for the time-to-first COPD exacerbation in the hdPS-matched cohort during the prespecified study period (1 April 2015 to 31 March 2019). CI, confidence interval; COPD, chronic obstructive pulmonary disorder; hdPS, high-dimensional propensity score; HR, hazard ratio; SA, sensitivity analysis; Tio, tiotropium; Tio/Olo, tiotropium/olodaterol
Additional Fig. S2 Sensitivity analyses for the time-to-event for all-cause inpatient mortality, first MACE, and first use of home oxygen therapy in the hdPS-matched cohort during the prespecified study period (1 April 2015 to 31 March 2019). CI, confidence interval; hdPS, high-dimensional propensity score; HR, hazard ratio; MACE, major adverse cardiovascular event; SA, sensitivity analysis; Tio, tiotropium; Tio/Olo, tiotropium/olodaterol
### Additional Table S1a

**Patient selection in the primary and sensitivity analysis cohorts**

| Reason for exclusion | Primary analysis cohort | Sensitivity analysis 1 | Sensitivity analysis 2 | Sensitivity analysis 3 | Sensitivity analysis 4 | Sensitivity analysis 5 |
|----------------------|-------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
|                      | Study period to 31 March 2019 | Excluded | Remaining | Excluded | Remaining | Excluded | Remaining | Excluded | Remaining | Excluded | Remaining | Excluded | Remaining | Excluded | Remaining | Excluded | Remaining | Excluded | Remaining | Excluded | Remaining | Excluded | Remaining |
| All patients         | 29,604,920              |            | 31,898,947 | 29,604,920 |            | 29,604,920 |            | 29,604,920 |            | 29,604,920 |            | 29,604,920 |
| Did not meet cohort entry criteria | 261,545,865,550,440 | 31,625,413 | 36,934 | 260,546,861,771 | 88,148 | 260,546,861 | 85,340 | 260,546,861 | 85,340 | 260,546,861 | 85,340 | 260,546,861 |
| ≥ 180 days continuous enrolment during BL period | 10,461 | 43,579 | 13,318 | 85,716 | 26,992 | 81,197 | 10,461 | 43,579 | 13,318 | 85,716 | 26,992 | 81,197 |
| Previous use of Tio/Olo or Tio before cohort entry | 132,435 | 14,234 | 43,922 | 15,894 | 16,050 | 43,107 | 32,145 | 12,434 | 32,145 | 12,434 | 43,922 | 15,894 |
| Age < 40 years at cohort entry | 1147 | 12,287 | 1189 | 15,765 | 873 | 42,234 | 1147 | 12,287 | 1147 | 12,287 | 1147 | 12,287 |
| Any LAMA/LABA/ICS maintenance therapy > 30 days during BL period | 1784 | 10,503 | 2257 | 13,448 | 9459 | 32,775 | 1784 | 10,503 | 1784 | 10,503 | 1784 | 10,503 |
| Any LAMA/LABA/ICS maintenance therapy within 30 days of cohort entry | 10,503 | 13,448 | 0 | 52,775 | 10,503 | 1 | 10,503 | 1 | 10,503 | 1 | 10,503 | 1 |
| No prior diagnosis COPD from the start of all available data until 1 day before cohort entry | 2985 | 7518 | 4115 | 9333 | 16,414 | 16,361 | 2985 | 7518 | 2985 | 7518 | 2985 | 7518 |
| Asthma diagnosis during BL period | 367 | 7151 | 493 | 6948 | 1745 | 14,616 | 367 | 7151 | 367 | 7151 | 367 | 7151 |
| Lung cancer diagnosis from the start of all available data until 1 day before cohort entry | 361 | 6790 | 468 | 8380 | 1928 | 12,688 | 361 | 6790 | 361 | 6790 | 361 | 6790 |
| Lung transplant from the start of all available data until 1 day before cohort entry | 0 | 6790 | 0 | 12,688 | 0 | 12,688 | 0 | 12,688 | 0 | 12,688 | 0 | 12,688 |
| Initiated Tio/Olo and Tio simultaneously at cohort entry | 1 | 6789 | 17 | 8373 | 14 | 12,674 | 1 | 6789 | 1 | 6789 | 1 | 6789 |
| Use of any triple therapy during BL period or between cohort entry and 1 day before the start of the follow-up period | 1 | 6788 | 8 | 8365 | 5 | 12,669 | 1 | 6788 | 1 | 6788 | 1 | 6788 |
| Final cohort | - | 6788 | 8 | 8365 | 5 | 12,669 | - | 6788 | - | 6784 | - | 6788 |
| Tio group | - | 5352 | 6505 | - | 10,388 | - | 5352 | - | 5349 | - | 5883 | - | 5352 |
| Tio/Olo group | - | 1436 | 1860 | - | 2281 | - | 1436 | - | 1435 | - | 1605 | - | 1436 |

**Sensitivity analysis 1**: this cohort only included patients with one prescription for an index medication (rather than two prescriptions within 60 days)

**Sensitivity analysis 2**: as-treated cohort

**Sensitivity analysis 3**: this cohort only included patients with the COPD ICD-10 codes J43 and J44 and excluded those with the ICD-10 code J41 (chronic bronchitis)

**Sensitivity analysis 4**: this cohort included patients with COPD and a diagnosis code for asthma but no prescriptions for asthma-specific treatment

**Sensitivity analysis 5**: this cohort censored data for patients with evidence of asthma on the date of the asthma diagnosis during the follow-up period

*Triple therapy included any fixed-dose or concurrent use of LAMA, LABA, or ICS

BL, baseline; COPD, chronic obstructive pulmonary disorder; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision; ICS, inhaled corticosteroid; LABA, long-acting β₂-agonist; LAMA, long-acting muscarinic antagonist; Tio, tiotropium; Tio/Olo, tiotropium/olodaterol
### Additional Table S1b

**Patient selection in the sensitivity analysis cohorts for the post hoc extension study period (from 28 September 2015 to 31 March 2020)**

| Reason for exclusion                              | Sensitivity analysis 1 | Sensitivity analysis 2 | Sensitivity analysis 3 | Sensitivity analysis 4 | Sensitivity analysis 5 |
|--------------------------------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
| Study period to 31 March 2020                    | Excluded               | Remaining              | Excluded               | Remaining              | Excluded               | Remaining              |
| All patients                                     | 31,898,947             | 31,898,947             | 31,898,947             | 31,898,947             | 31,898,947             | 31,898,947             |
| Did not meet cohort entry criteria               | 31,790,245             | 108,702                | 31,829,413             | 69,702                 | 31,829,418             | 69,534                 |
| Excluded                                         | 25,768                 | 82,934                 | 13,818                 | 55,716                 | 13,818                 | 55,716                 |
| Previous use of Tio/Olo or Tio before cohort entry | 47,773                 | 35,161                 | 39,822                 | 15,894                 | 39,825                 | 15,886                 |
| Excluded                                         | 559                    | 94,002                 | 189                    | 15,697                 | 189                    | 15,705                 |
| Age < 40 years at cohort entry                   | 4827                   | 2267                   | 3,448                  | 2267                   | 3,448                  | 2,257                  |
| Excluded                                         | 4827                   | 2267                   | 3,448                  | 2267                   | 3,448                  | 2,257                  |
| Any LAMA/LABA/ICS maintenance therapy within 30 days of cohort entry | 0                     | 20,775                 | 0                      | 1,448                  | 0                      | 1,448                  |
| Excluded                                         | 11,866                 | 17,909                 | 4115                   | 9333                   | 4117                   | 9323                   |
| Asthma diagnosis during BL period                | 1206                   | 19,703                 | 488                    | 938                    | 109                    | 974                    |
| Excluded                                         | 1161                   | 15,542                 | 468                    | 8380                   | 468                    | 8380                   |
| Lung cancer diagnosis from the start of all available data until 1 day before cohort entry | 0                     | 15,542                 | 0                      | 9380                   | 0                      | 9380                   |
| Excluded                                         | 0                      | 15,542                 | 0                      | 9380                   | 0                      | 9380                   |
| Initiated Tio/Olo and Tio simultaneously at cohort entry | 10                   | 15,532                 | 17                     | 9373                   | 2                      | 9368                   |
| Excluded                                         | 18                     | 15,514                 | 18                     | 9365                   | 18                     | 9360                   |
| Use of any triple therapy during BL period or between cohort entry and 1 day before the start of the follow-up period | 18                   | 15,514                 | 18                     | 9365                   | 18                     | 9360                   |
| Final cohort                                     | 15,514                 | 8365                   | 8360                   | 9228                   | 8365                   |
| Tio group                                        | 12,208                 | 6505                   | 6502                   | 7164                   | 6505                   |
| Tio/Olo group                                    | 3306                   | 1860                   | 1858                   | 2064                   | 1860                   |

**Sensitivity analysis 1**: this cohort only included patients with one prescription for an index medication (rather than two prescriptions within 60 days)

**Sensitivity analysis 2**: as-treated cohort

**Sensitivity analysis 3**: this cohort only included patients with the COPD ICD-10 codes J43 and J44 and excluded those with the ICD-10 code J41 (chronic bronchitis)

**Sensitivity analysis 4**: this cohort included patients with COPD and a diagnosis code for asthma but no prescription for asthma‐specific treatment

**Sensitivity analysis 5**: this cohort censored data for patients with evidence of asthma on the date of the asthma diagnosis during the follow-up period

*Triple therapy included any fixed-dose or concurrent use of LAMA, LABA, or ICS

BL, baseline; COPD, chronic obstructive pulmonary disorder; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision; ICS, inhaled corticosteroid; LABA, long-acting β₂-agonist; LAMA, long-acting muscarinic antagonist; Tio, tiotropium; Tio/Olo, tiotropium/olodaterol
### Additional Table S2

Sensitivity analyses for escalation to triple therapy (fixed-dose or concurrent ICS/LAMA/LABA) during the prespecified study period (from 28 September 2015 to 31 March 2019)

| Variable | Sensitivity analysis 1 | Sensitivity analysis 2 | Sensitivity analysis 3 | Sensitivity analysis 4 | Sensitivity analysis 5 |
|----------|------------------------|------------------------|------------------------|------------------------|------------------------|
|          | Tio                    | Tio/Olo                | Tio                    | Tio/Olo                | Tio                    |
| Number of patients | 2183                   | 2183                   | 1317                   | 1317                   | 1304                   |
| Number of escalation events | 15                     | 11                     | 1                      | 0                      | 11                     |
| Number of patient-years | 1475                   | 1452                   | 240                    | 214                    | 924                    |
| HR for time-to-escalation (95% CI) | 0.74 (0.34–1.61)       | NC                     | 0.65 (0.25–1.69)       | 1.37 (0.47–3.95)       | 2.07 (0.38–11.31)      |

**hdPS-matched cohort**

| Variable | Sensitivity analysis 1 | Sensitivity analysis 2 | Sensitivity analysis 3 | Sensitivity analysis 4 | Sensitivity analysis 5 |
|----------|------------------------|------------------------|------------------------|------------------------|------------------------|
|          | Tio                    | Tio/Olo                | Tio                    | Tio/Olo                | Tio                    |
| Number of patients | 10,388                 | 2281                   | 5352                   | 1436                   | 5349                   |
| Number of escalation events | 54                     | 15                     | 13                     | 0                      | 30                     |
| Number of patient-years | 8003                   | 1508                   | 1178                   | 228                    | 4178                   |
| HR for time-to-escalation (95% CI) | 1.44 (0.81–2.54)       | NC                     | 1.11 (0.51–2.43)       | 1.17 (0.58–2.36)       | 0.98 (0.37–2.59)       |

**Unmatched cohort**

| Variable | Sensitivity analysis 1 | Sensitivity analysis 2 | Sensitivity analysis 3 | Sensitivity analysis 4 | Sensitivity analysis 5 |
|----------|------------------------|------------------------|------------------------|------------------------|------------------------|
|          | Tio                    | Tio/Olo                | Tio                    | Tio/Olo                | Tio                    |
| Number of patients | 10,388                 | 2281                   | 5352                   | 1436                   | 5349                   |
| Number of escalation events | 54                     | 15                     | 13                     | 0                      | 30                     |
| Number of patient-years | 8003                   | 1508                   | 1178                   | 228                    | 4178                   |
| HR for time-to-escalation (95% CI) | 1.44 (0.81–2.54)       | NC                     | 1.11 (0.51–2.43)       | 1.17 (0.58–2.36)       | 0.98 (0.37–2.59)       |

**Sensitivity analysis 1:** this cohort only included patients with one prescription for an index medication (rather than two prescriptions within 60 days)

**Sensitivity analysis 2:** as-treated cohort

**Sensitivity analysis 3:** this cohort only included patients with the COPD ICD-10 codes J43 and J44 and excluded those with the ICD-10 code J41 (chronic bronchitis)

**Sensitivity analysis 4:** this cohort included patients with COPD and a diagnosis code for asthma but no prescriptions for asthma-specific treatment

**Sensitivity analysis 5:** this cohort censored data for patients with evidence of asthma on the date of the asthma diagnosis during the follow-up period

CI, confidence interval; COPD, chronic obstructive pulmonary disorder; hdPS, high-dimensional propensity score; HR, hazard ratio; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision; ICS, inhaled corticosteroid; LABA, long-acting β₂-agonist; LAMA, long-acting muscarinic antagonist; NC, not calculable; Tio, tiotropium; Tio/Olo, tiotropium/olodaterol
Additional Fig. S1
Sensitivity analyses for the time-to-first COPD exacerbation in the hdPS-matched cohort during the prespecified study period (1 April 2015 to 31 March 2019). CI, confidence interval; COPD, chronic obstructive pulmonary disorder; hdPS, high-dimensional propensity score; HR, hazard ratio; SA, sensitivity analysis; Tio, tiotropium; Tio/Olo, tiotropium/olodaterol.
Additional Fig. S2
Sensitivity analyses for the time-to-event for all-cause inpatient mortality, first MACE, and first use of home oxygen therapy in the hdPS-matched cohort during the prespecified study period (1 April 2015 to 31 March 2019). CI, confidence interval; hdPS, high-dimensional propensity score; HR, hazard ratio; MACE, major adverse cardiovascular event; SA, sensitivity analysis; Tio, tiotropium; Tio/Olo, tiotropium/olodaterol

|                  | All-cause inpatient mortality | MACE | Home oxygen therapy |
|------------------|-------------------------------|------|---------------------|
| **HR (95% CI)**  | 1.00 (0.78–1.30)              | 0.97 (0.83–1.12) | 1.17 (1.02–1.33)    |
| **SA 1**         | 0.45 (0.22–0.90)              | 0.90 (0.66–1.24) | 1.08 (0.90–1.29)    |
| **SA 2**         | 0.88 (0.64–1.21)              | 0.86 (0.72–1.04) | 0.99 (0.84–1.16)    |
| **SA 3**         | 0.69 (0.52–0.93)              | 0.89 (0.75–1.06) | 1.02 (0.87–1.19)    |
| **SA 4**         | 0.82 (0.59–1.12)              | 0.86 (0.71–1.04) | 1.09 (0.92–1.29)    |
| **SA 5**         |                               |      |                     |

Favours Tio/Olo  Favours Tio  Favours Tio/Olo  Favours Tio  Favours Tio/Olo  Favours Tio