a) Primary end points: US hypothesis testing strategy

The primary end-point comparisons for Tio + Olo FDC (5/5 µg) will be analysed first in the following order:

1. Superiority in mean FEV_1 AUC_{0-3} response in patients treated with Tio + Olo FDC (5/5 µg) compared to patients treated with Olo (5 µg), after 24 weeks (individual study data sets)
2. Superiority in mean FEV_1 AUC_{0-3} response in patients treated with Tio + Olo FDC (5/5 µg) compared to patients treated with Tio (5 µg), after 24 weeks (individual study data sets)
3. Superiority in mean FEV_1 trough response in patients treated with Tio + Olo FDC (5/5 µg) compared to patients treated with Olo (5 µg), after 24 weeks (individual study data sets)
4. Superiority in mean FEV_1 trough response in patients treated with Tio + Olo FDC (5/5 µg) compared to patients treated with Tio (5 µg), after 24 weeks (individual study data sets)

If the above tests are positive, the primary end-point comparisons for Tio + Olo FDC (2.5/5 µg) will then be analysed in the following order:

5. Superiority in mean FEV_1 AUC_{0-3} response in patients treated with Tio + Olo FDC (2.5/5 µg) compared to patients treated with Olo (5 µg), after 24 weeks (individual study data sets)
6. Superiority in mean FEV_1 AUC_{0-3} response in patients treated with Tio + Olo FDC (2.5/5 µg) compared to patients treated with Tio (2.5 µg), after 24 weeks (individual study data sets)
7. Superiority in mean FEV_1 trough response in patients treated with Tio + Olo FDC (2.5/5 µg) compared to patients treated with Olo (5 µg), after 24 weeks (individual study data sets)
8. Superiority in mean FEV_1 trough response in patients treated with Tio + Olo FDC (2.5/5 µg) compared to patients treated with Tio (2.5 µg), after 24 weeks (individual study data sets)
9. Superiority in mean FEV_1 AUC_{0-3} response in patients treated with Tio + Olo FDC (2.5/5 µg) compared to patients treated with Tio (5 µg), after 24 weeks (individual study data sets)
10. Superiority in mean FEV_1 trough response in patients treated with Tio + Olo FDC (2.5/5 µg) compared to patients treated with Tio (5 µg), after 24 weeks (individual study data sets)

b) Primary end points: EU hypothesis testing strategy

The primary end-point comparisons for Tio + Olo FDC (5/5 µg) will be analysed first in the following order:

1. Superiority in mean FEV_1 AUC_{0-3} response in patients treated with Tio + Olo FDC (5/5 µg) compared to patients treated with Olo (5 µg), after 24 weeks (individual study data sets)
2. Superiority in mean FEV_1 AUC_{0-3} response in patients treated with Tio + Olo FDC (5/5 µg) compared to patients treated with Tio (5 µg), after 24 weeks (individual study data sets)
3. Superiority in mean FEV_1 trough response in patients treated with Tio + Olo FDC (5/5 µg) compared to patients treated with Olo (5 µg), after 24 weeks (individual study data sets)
4. Superiority in mean FEV_1 trough response in patients treated with Tio + Olo FDC (5/5 µg) compared to patients treated with Tio (5 µg), after 24 weeks (individual study data sets)
5. Superiority in mean SGRQ total score in patients treated with Tio + Olo FDC (5/5 µg) compared to patients treated with Olo (5 µg), after 24 weeks (combined data set)
6. Superiority in mean SGRQ total score in patients treated with Tio + Olo FDC (5/5 µg) compared to patients treated with Tio (5 µg), after 24 weeks (combined data set)

If the above tests are positive, the primary end-point comparisons for Tio + Olo FDC (2.5/5 µg) will then be analysed in the following order:

7. Superiority in mean FEV_1 AUC_{0-3} response in patients treated with Tio + Olo FDC (2.5/5 µg) compared to patients treated with Olo (5 µg), after 24 weeks (individual study data sets)
8. Superiority in mean FEV_1 AUC_{0-3} response in patients treated with Tio + Olo FDC (2.5/5 µg) compared to patients treated with Tio (2.5 µg), after 24 weeks (individual study data sets)
9. Superiority in mean FEV_1 trough response in patients treated with Tio + Olo FDC (2.5/5 µg) compared to patients treated with Olo (5 µg), after 24 weeks (individual study data sets)
10. Superiority in mean FEV_1 trough response in patients treated with Tio + Olo FDC (2.5/5 µg) compared to patients treated with Tio (2.5 µg), after 24 weeks (individual study data sets)
11. Superiority in mean SGRQ total score in patients treated with Tio + Olo FDC (2.5/5 µg) compared to patients treated with Olo (5 µg), after 24 weeks (combined data set)
12. Superiority in mean SGRQ total score in patients treated with Tio + Olo FDC (2.5/5 µg) compared to patients treated with Tio (2.5 µg), after 24 weeks (combined data set)

c) Key secondary end point

The secondary end point will be analysed in the following order. Each test will be considered confirmatory only if (i) all key primary end points are successful and (ii) all previous key secondary end-point tests are successful:

1. Superiority in mean TDI total score in patients treated with Tio + Olo FDC (5/5 µg) compared to patients treated with Olo (5 µg), after 24 weeks (combined data sets)
2. Superiority in mean TDI total score in patients treated with Tio + Olo FDC (5/5 µg) compared to patients treated with Tio (5 µg), after 24 weeks (combined data sets)
3. Superiority in mean TDI total score in patients treated with Tio + Olo FDC (2.5/5 µg) compared to patients treated with Olo (5 µg), after 24 weeks (combined data sets)
4. Superiority in mean TDI total score in patients treated with Tio + Olo FDC (2.5/5 µg) compared to patients treated with Tio (2.5 µg), after 24 weeks (combined data sets)

d) Further tests in the EU hypothesis testing strategy

1. Superiority in mean FEV_1 AUC_{0-3} response in patients treated with Tio + Olo FDC (2.5/5 µg) compared to patients treated with Tio (5 µg), after 24 weeks (individual study data sets)
2. Superiority in mean FEV_1 trough response in patients treated with Tio + Olo FDC (2.5/5 µg) compared to patients treated with Tio (5 µg), after 24 weeks (individual study data sets)
3. Superiority in mean SGRQ total score in patients treated with Tio + Olo FDC (2.5/5 µg) compared to patients treated with Tio (5 µg), after 24 weeks (combined data set)
4. Superiority in mean TDI focal score in patients treated with Tio + Olo FDC (2.5/5 µg) compared to patients treated with Tio (5 µg), after 24 weeks (combined data set)