Background:
There is limited experience about the longitudinal effects of oral first-line MS treatments on cognition, behavioral and clinical outcomes under real-life conditions, although cognition, fatigue and depression are important indicators and predictive factors for disease progression.

Objectives:
(1) To longitudinally assess clinical, cognitive and behavioral profiles in RRMS patients being orally treated with teriflunomide (TFL; Aubagio®) as first-line therapy (de novo/DNG) or changing from other MS therapies (switchers/SWG)
(2) To evaluate differences in therapeutic outcomes between de novos and switchers
(3) To check for differences in test/re-test effects between RRMS and normative controls.

Methods:
Retrospective, multicenter, open-label registry data analysis from 35 German MS practices (NTD network). Data was available at baseline (T0) and after 12 months (T12) identifying 293 TFL-treated patients (McDonald; mean age: 48.4 yr, 67.2% female, mean EDSS 2.3) that had completed a 12-month treatment period. Among them were 96 (32.7%) de-novos (DNG) and 197 (67.3%) switchers (SWG) coming from various medications (Ref. Fig.1+2) Outcomes: Clinical status (EDSS), IQ (MWI-B), cognition indexed by (1) information processing speed and capacity (SDMT), (2) verbal (CVLT) and visuo-spatial memory (BVMT-R) from BICAMS battery, (2) interference control (Stroop), (3) fluency (RWT), and PROs represented by motor and cognitive fatigue (FMC), depression (BDI-FS, fast screen) and QoL (EQ-SD).

Results:
At baseline (T0), RRMS patients performed insignificantly below the arithmetic mean of normative controls in cognitive testing. Motor fatigue scored at a medium, cognitive fatigue at a low level, depression in the normal range.

Across 12 months (T12:T0), 86.4% of all RRMS patients remained relapse-free and EDSS stable (2.3 vs. 2.4), as did BICAMS parameters (SDMT, CVLT, BVMT-R) and all 4 dimensions of fluency (RWT), i.e., formal-lexical, semantic fluency, formal-lexical and semantic category change). Interference processing significantly improved over time (p<0.01). Depression distinctly increased (2.3 vs. 2.8, p<0.04), without reaching clinically relevant threshold (5.0). Motor FMC score persisted at a medium level (29.3), whereas cognitive fatigue, despite significantly augmenting (26.0 vs 27.4, p<0.04), remained on a low level.

When comparing de novos and switchers, baseline and longitudinal outcomes were generally better in DNG than SWG. EDSS worsened significantly more in SWG than NCG (p<0.001; Ref. Fig. 3), and significant cognitive improvement was found in DNG vs. SWG for non-verbal memory (BVMT: p<0.03; Ref. Fig.4) and lexical fluency (RWT-FW, RWT-FLK: p<0.004; Ref. Fig.5) while SWG only improved in interference processing time (p<0.002), however starting from a significantly lower base level than DNG. Positive test/re-test effects of cognitive variables were present in RRMS patients but less dynamic than in normative control groups.

Conclusion:
(1) Teriflunomide has the potential to stabilize/improve clinical course and cognition, but not behavioral outcomes in RRMS. (2) Switchers take less benefit from TFL therapy than de novo patients highlighting the importance of early treatment onset (3) Positive test/re-test effects are expressed to a lower degree in RRMS patients than normative controls.