SUPPLEMENTAL INFORMATION

Clinical response evaluation in treatment-resistant depression patients 4 weeks after starting a new treatment – Interim analysis of the ResisToday Study

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Major Depressive Disorder (MDD) and Treatment-Resistant Depression (TRD)

- MDD is a complex and recurrent psychiatric illness[1]
- About **one third of patients fail to achieve remission**
  - When they do not respond adequately to two consecutive treatments, with two different antidepressants at an adequate dose and duration, they are considered to meet criteria for TRD[1,2]

- Systematically characterizing MDD patients may enable an earlier and more accurate identification of TRD patients[3]
- Since in Portugal the TRD patient population is poorly characterized, we carried out ResisToday study

Adapted from: Harvard.edu, Assessment and Treatment of Major Depressive Disorders.

1. Otte C, Gold SM, Penninx BW, et al., Major depressive disorder. *Nat Rev Dis Prim*. 2016;2:16065. doi:10.1038/nrdp.2016.65.
2. Limandri B., Treatment-Resistant Depression: Identification and Treatment Strategies. *J Psychosoc Nurs Ment Heal Serv*. 2018;56(9):11-15.
3. Gaynes B., Assessing the risk factors for difficult-to-treat depression and treatment-resistant depression. *J Clin Psychiatry.* 2016;77(Suppl 1):4-8.

IV Encontro das Secções; Moreira R et al.

ResisToday Study Design

- ResisToday is a prospective, multicenter, and **observational study to evaluate clinical response of TRD patients at 4 weeks and 20 weeks after starting a new treatment**, in Portugal
- 15 sites actively recruited the first 68 patients considered in this interim analysis
- A total of approximately 150 TRD patients will be recruited before the final analysis

Key eligibility criteria

- ≥ 18 years old
- Dx of single episode or recurrent MDD
- MDD with a Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥22 at baseline
- Meets/has met the TRD criteria
- Is initiating a new antidepressant treatment* to treat the current depressive episode.

Visit 1, baseline

- ICF signature
- Demographic and clinical profile
- Previous and current txt
- MADRS, CGI-S, PHQ-9, EQ 5D-5L
- Concomitant medication

Visit 2, 4 weeks

- Current txt
- MADRS, CGI-S, PHQ-9, EQ 5D-5L
- Concomitant medication
- AEs
- Medical resource utilization

Visit 3, 20 weeks

- Current txt
- MADRS, CGI-S, PHQ-9, EQ 5D-5L
- Concomitant medication
- AEs
- Medical resource utilization

TRD: treatment resistant depression; Dx: diagnostic; MDD: major depressive disorder; ICF: informed consent form; txt: treatments; MADRS: Montgomery-Åsberg Depression Rating Scale.

*In the context of this observational study, a new antidepressant treatment is considered any new pharmacological and/or non-pharmacological treatment that is prescribed to replace the existing antidepressant treatment or is prescribed in addition to (ie, on top of) the previously established antidepressant treatment with the intent to improve a patient's clinical depressive syndrome. Accordingly, any dose escalation of an antidepressant prescribed prior to baseline or the addition of any drug intended to increase the plasma-concentration of an antidepressant prescribed prior to baseline is not considered a new antidepressant treatment.

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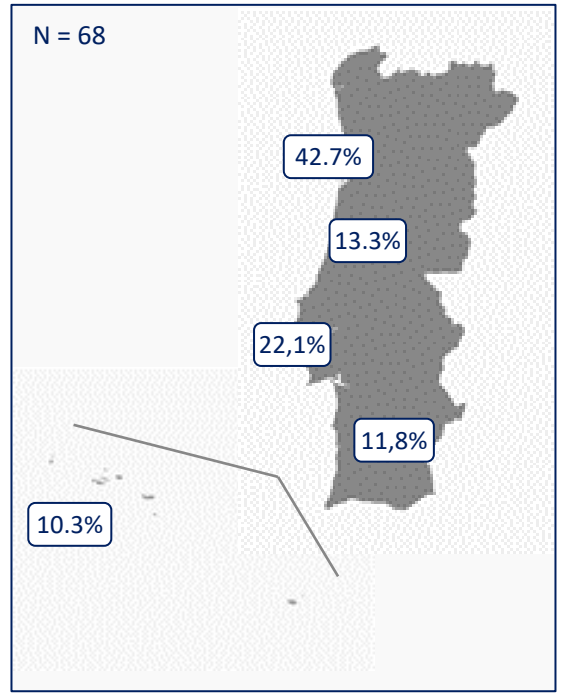
Patient Disposition

	Total
FAS dataset, n	68
CHU São João	5 (7.4%)
ULS Baixo Alentejo - Hospital José Joaquim Fernandes	3 (4.4%)
CHU Coimbra	1 (1.5%)
ULS Guarda (Consulta H. Guarda e H. Seia)	3 (4.4%)
CH Leiria - Hospital de Santo André	5 (7.4%)
CH Lisboa Ocidental - Hospital Egas Moniz	1 (1.5%)
Hospital do Divino Espírito Santo	7 (10.3%)
CHU Algarve - Hospital de Portimão	5 (7.4%)
Hospital Magalhães Lemos	4 (5.9%)
CH Setúbal - Hospital São Bernardo	1 (1.5%)
CH Oeste	11 (16.2%)
ULS Alto Minho - Hospital de Santa Luzia	3 (4.4%)
CH Vila Nova de Gaia/Espinho	4 (5.9%)
CH Psiquiátrico de Lisboa	2 (2.9%)
CH Póvoa de Varzim – Vila do Conde (Unidade de Vila do Conde)	13 (19.1%)



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Demographic and Other Baseline Characteristics

- Almost half of the patients (**48.5%**) were **not working** upon study entrance
- Patient's **psychiatric disorder** was **the reason that mostly impacted** their **employment/occupational status**
- Mean **duration of the current MDD episode was almost 2 years** (23.37 months)

	Total TRD Patients (n=68)
Age (years)	
Mean (SD) [range]	54.68 (9.98) [32-85]
Gender, n (%)	
Male	12 (17.6%)
Female	56 (82.4%)
Employment/occupational status, n (%)	
Employed	35 (51.5%)
Unemployed	12 (17.7%)
Other	21 (30.9%)
If employment / occupational status was impacted due to any reason, n (%)	
Psychiatric Disease	51 (92.7%)
Other Disease	2 (3.6%)
Other reason	2 (3.6%)
Age at diagnosis of MDD (years)[a)]	
Mean (SD) [range]	41.94 (13.72)[13-68]
Years since diagnosis of MDD (years)[a)]	
Mean (SD) [range]	12.79 (12.23) [0-55]
Duration of current MDD (months)[b)]	
Mean (SD) [range]	23.37 (22.04) [2-96]
Was this the first Major Depressive Episode?, n (%)	
No	51 (75%)
If no, number of previous episodes	
Mean (SD) [range]	3.53 (2.2) [2-11]
Previous MDD episodes mean duration (months), Mean (SD) [range]	13.74 (13.93) [1-84]
If no, does the patient have recurrent MDD episodes?	
Yes	43 (84.3%)

a) n=67; b) n=65.

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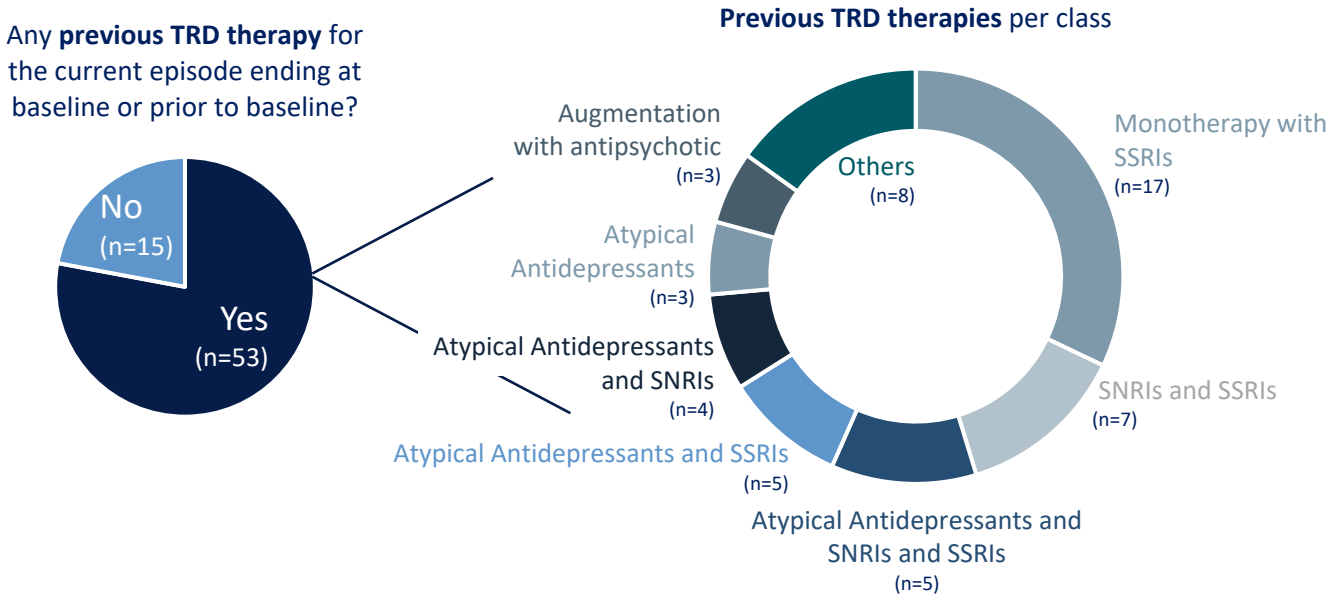
Baseline Characteristics – Previous TRD therapies (current episode)



	Total TRD Patients (n=68)
Previous TRD therapies[a], n (%)	
SSRIs	**62 (116.9%)**
Escitalopram	20 (37.7%)
Sertraline	18 (34.0%)
Fluoxetine	11 (20.8%)
Paroxetine	5 (9.4%)
Vortioxetine	4 (7.6%)
Fluvoxamine	3 (5.7%)
SNRIs	**21 (39.6%)**
Venlafaxine	14 (26.4%)
Duloxetine	7 (13.2%)
Atypical Antidepressants	**23 (43.4%)**
Bupropion	13 (24.5%)
Mirtazapine	5 (9.4%)
Trazodone	3 (5.7%)
Augmentation with antipsychotic	**9 (16,9%)**
Quetiapine	4 (7.6%)
Others	**5 (9.4%)**

a) Patients may have received more than one previous TRD therapy.

- SSRIs were used in 41 previous lines (77,4%), in several combinations
- Treatment strategies were notably heterogeneous

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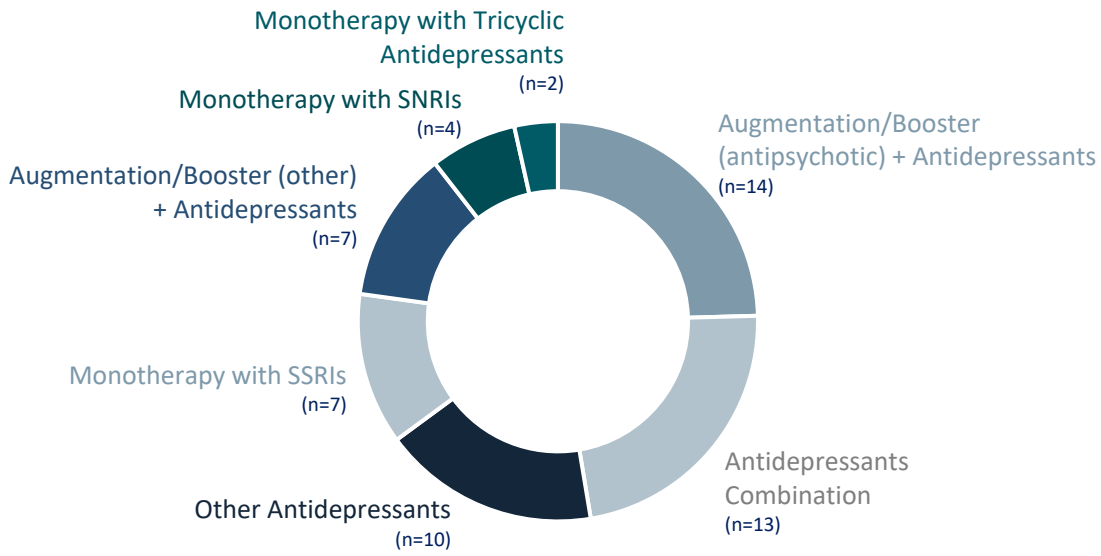
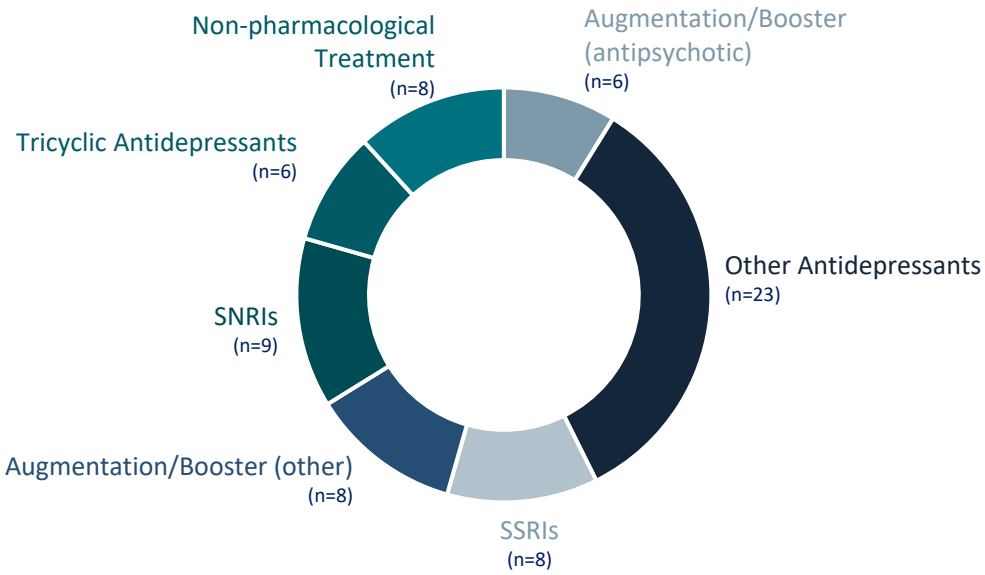
TRD Therapies and Concomitant Treatments Ongoing and Initiated at Baseline, per drug class

TRD Therapies per class Ongoing at Baseline



TRD Therapies per class/no pharmacological treatment Initiated at Baseline



- Most patients were being treated w/ Augmentation/Boosters (antipsychotics) + Antidepressants (n=14, 41.2%) and Antidepressant Combinations (n=13, 38%) upon study entrance
- A sizable portion of patients initiated other antidepressants (n=23, 33,8%) upon study entrance

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TRD Therapies and Concomitant Treatments Ongoing and Initiated at Baseline

	Ongoing at Baseline	Initiated at Baseline
TRD therapies[a], n (%)		
Atypical Antidepressants	**38 (55.9%)**	**23 (33.8%)**
Mirtazapine	20 (29.4%)	11 (16.2%)
Bupropion	6 (8.8%)	7 (10.3%)
Trazodone	12 (17.6%)	0 (0%)
SNRIs	**21 (30.9%)**	**9 (13.2%)**
Venlafaxine	18 (26.5%)	9 (13.2%)
Augmentation with Antipsychotic	**18 (26.5%)**	**7 (10.3%)**
Quetiapine	13 (19.1%)	0 (0%)
Aripiprazole	1 (1.5%)	6 (8.8%)
SSRIs	**22 (32.4%)**	**10 (14.7%)**
Vortioxetine	5 (7.4%)	6 (8.8%)
Fluoxetine	8 (11.8%)	0 (0%)
Sertaline	7 (10.3%)	0 (0%)
Tricyclic Antidepressants	**7 (10.3%)**	**4 (5.9%)**
Clomipramine	5 (7.4%)	4 (5.9%)
Augmentation with Mood Stabilizer	**4 (5.9%)**	**3 (4.4%)**
Lamotrigine	4 (5.9%)	3 (4.4%)
Non-Pharmacological Treatment[b]	**0 (0%)**	**8 (11.8%)**
Others	0 (0%)	4 (5.9%)

a) Patients may have received more than one TRD therapy; b) 7 psychotherapy + 1 electroconvulsive therapy.

- Trazodone was maintained, but not initiated at baseline
- Quetiapine was maintained, but not initiated at baseline
- Fluoxetine was maintained, but not initiated at baseline
- Sertaline was maintained, but not initiated at baseline
- Venlafaxine more common as ongoing, but initiated at baseline as frequently
- Non-pharmacological treatments were only initiated at baseline

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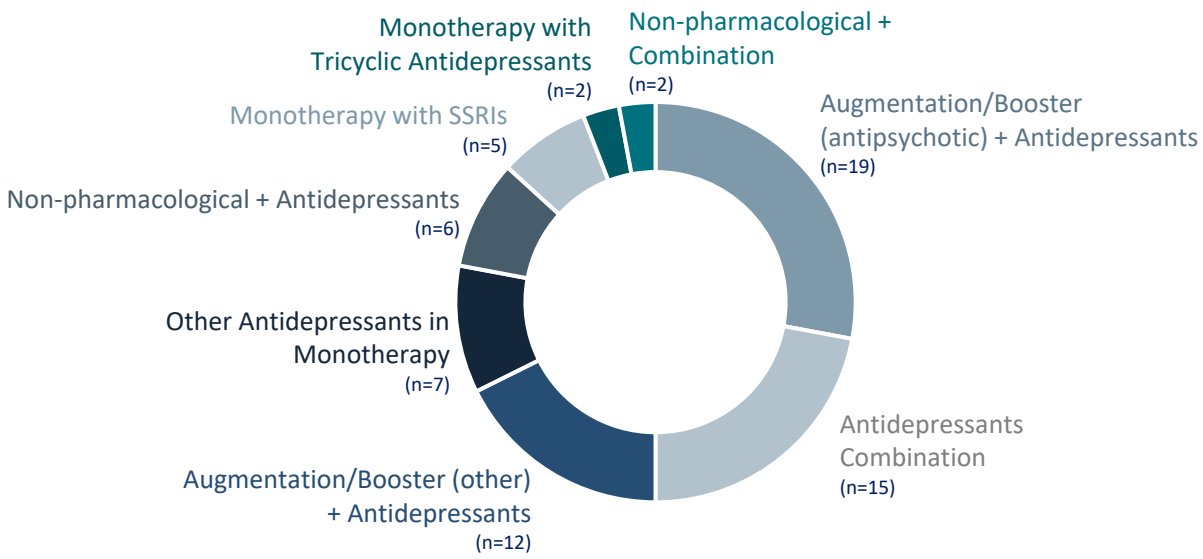
TRD Therapies and Concomitant Treatments Initiated, or Ongoing, at Baseline

TRD Therapies per class/no pharmacological treatment



	Total TRD Patients (n=68)
TRD therapies[a], n (%)	
Atypical Antidepressants	**60 (88.2%)**
Mirtazapine	31 (45.6%)
Bupropion	13 (19.1%)
Trazodone	12 (17.6%)
SNRIs	**30 (44.1%)**
Venlafaxine	27 (39.7%)
Augmentation with Antipsychotic	**26 (38.2%)**
Quetiapine	13 (19.1%)
SSRIs	**30 (44.1%)**
Vortioxetine	11 (16.2%)
Fluoxetine	8 (11.8%)
Tricyclic Antidepressants	**14 (20.6%)**
Clomipramine	9 (13.2%)
Non-Pharmacological Treatment[b]	**8 (11.8%)**
Others	10 (14.7%)

a) Patients may have received more than one TRD therapy. b) 7 psychotherapy + 1 electroconvulsive therapy.

- Most patients (67.6%) were treated with either:
  - Augmentation/Booster (antipsychotic)
  - Antidepressants Combination
  - Other Augmentation/Booster Strategy

- Mirtazapine and Venlafaxine were the most used treatments (in 31/68 and in 27/68 patients, respectively)

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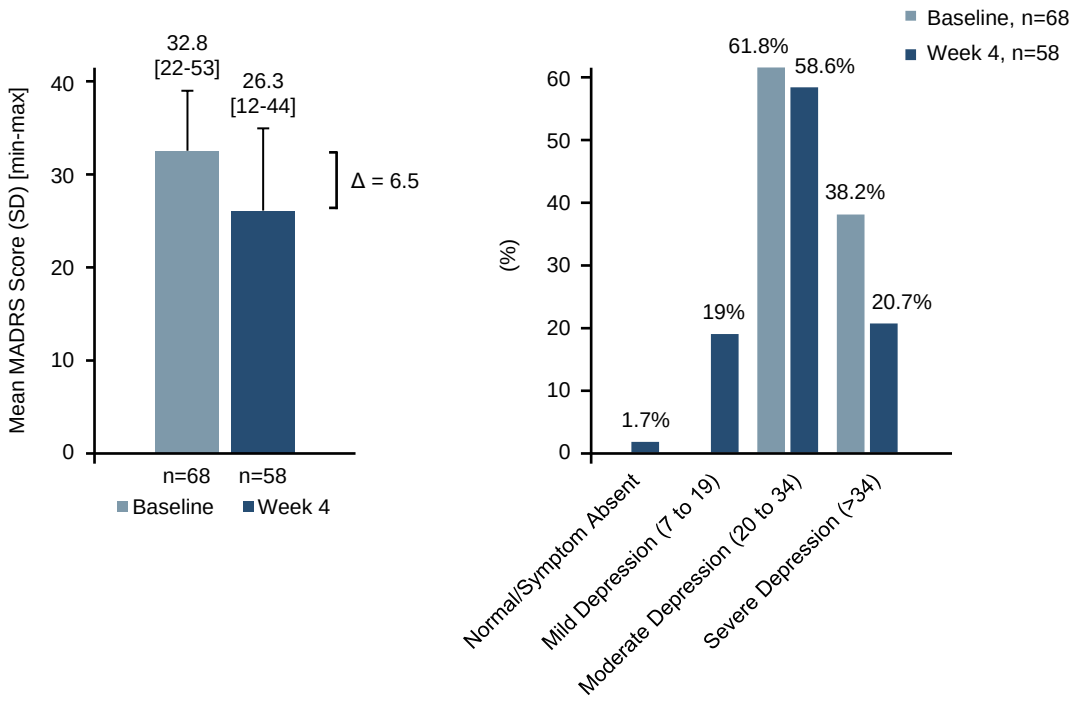
Clinical Outcomes – MADRS: Baseline *vs.* Week 4

- At baseline, the mean value of MADRS score was 32.8 points (range: 22 to 53 points) and at week 4 (n=58 patients with available MADRS score) was 26.3 points, ranging between 3 and 44 points – representing **a drop of 6.5 points**
- At week 4, the **mean percentual change in score from baseline was -19.1%** (n=58, $p < 0.001$)



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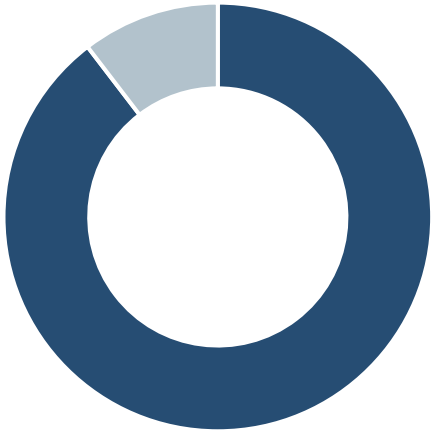
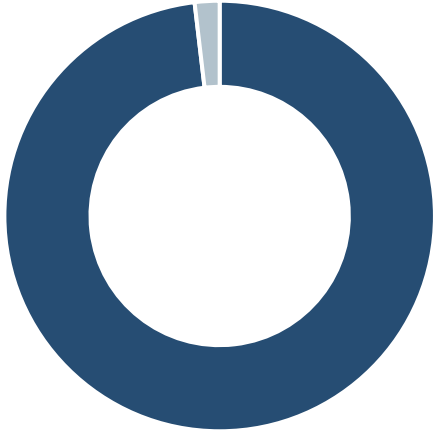
Clinical Outcomes – Clinical Response/CGI-S: Baseline *vs.* Week 4

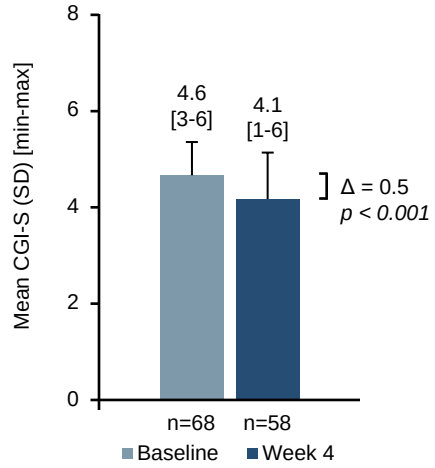
- **Clinical response was achieved by 10.4%** (7 out of 67; 95%CI: 4.3% to 20.3%) **of the patients**
- At week 4, **one patient** (out of 58, 1.7%) **was in remission**
- Mental health of patients at baseline (n=68) ranged between 3 (mildly ill) and 6 (severely ill), being, on average, **4.6 points. After 4 weeks** (n=58) the mean **CGI-S value was 4.1 points**
  - Mean reduction was 0.5 points and statistically significant (p<0.001)

Clinical Response: 10.4% (n=7)



Remissions: 1.7% (n=1)

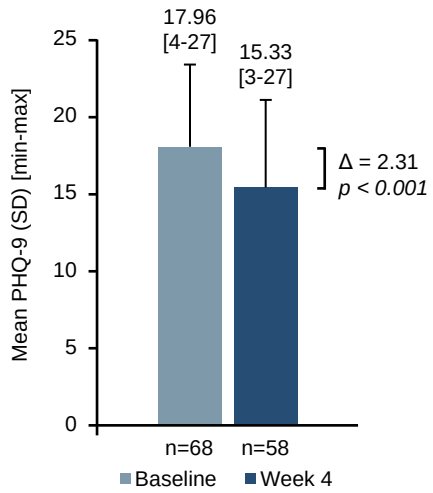


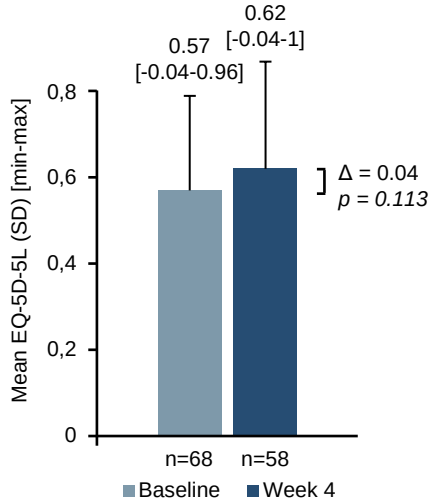


*Clinical Response rate at week 4, was defined as ≥50% improvement in the MADRS total score from baseline to a 4-week follow up, and reemission rate at week 4, was defined as a MADRS total score ≤10.
CGI-S: Clinical Global Impression of Severity.

Patient Reported Outcomes – PHQ-9/EQ-5D: Baseline *vs.* Week 4

- PHQ-9 mean values were 18.0 points (n=68), at baseline, and 15.3 (n=58) points at week 4
  - The mean reduction of 2.3 points was statistically significant (p<0.001)
- EQ-5D-5L score was 0.57 points at baseline and 0.62 at week 4
  - The mean change was 0.04 and was not statistically significant (p=0.113)





*PHQ-9: Patient Health Questionnaire-9.

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Conclusions

- A total of 68 patients were considered in this interim analysis
- At week 4, although statistically significant, a -19.1% reduction in MADRs score was measured, but **only 10.4% of patients achieved a clinical response** (representing a mean drop of 6.5 points)
  - Only 1 patient was in remission at week 4
- These results coincide with previous studies[1], showing a limited percentage of TRD patients achieving a clinical response, or remission, to current treatment strategies
- Also in the Portuguese setting, there is a need for more rapid disease control and effective treatment strategies, so that TRD patients may achieve fast clinical responses and remissions, while improving their QoL
- We expect to enroll 150 patients, and a final analysis will clarify how patient's clinical response evolves from week 4 to week 20

Key Findings

- After 4 weeks of treatment, 10.4% of the TRD patients achieved a clinical response (95% CI: 4.3% to 20.3%)
- 1 out of 68 was in remission
- There is a need for more rapid disease control and effective treatment strategies

IV Encontro das Secções; Moreira R et al.

Acknowledgments

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