TITLE: Prospective analysis of a TRD cohort over a 1-year follow-up with standard of care in Mexico: results for depression severity, treatment response, disability and QoL from the multicenter, observational TRAL Study

Titulo: Análisis prospectivo de una cohorte de TRD durante un seguimiento de 1 año con atención estándar en México: resultados para la gravedad de la depresión, la respuesta al tratamiento, la discapacidad y la CdV del Estudio TRAL multicéntrico y observacional.

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Short Title: Prospective follow-up of TRD patients in Mexico

Título corto: Seguimiento prospectivo de pacientes con TRD en México

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Conflict of Interest

1. JZ: declares no conflict of interests
2. JLVH: declares no conflict of interests
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4. LDAS: researcher for "Avalon-Vinculación Médica en Salud Mental", in which he is the principal investigator and sub-investigator of several protocols of original epidemiological research of the institution. Has received professional fees for the time spent on subject interviews in the present study by Janssen Research & Development, as approved by the Independent Research Ethics Committee. Dr. Alviso has work as speaker, collaborated in advisory boards, or received scientific fees from: Janssen, Pfizer, Sanofi Aventis, Schwabe-Pharma, Novartis, Lundbeck, Roche, Lilly, Asofarma, Psicofarma, Ferrer, Servier, and Shire
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Author Contribution

All authors contributed significantly to the design of the study and interpretation of the data. All the authors reviewed the final manuscript and approved the content.

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1 **TITLE: Prospective analysis of a TRD cohort over a 1-year**
2 **follow-up with standard of care in Mexico: results for**
3 **depression severity, treatment response, disability and QoL from**
4 **the multicenter, observational TRAL Study**

5 **Titulo: Análisis prospectivo de una cohorte de TRD durante un**
6 **seguimiento de 1 año con atención estándar en México: resultados**
7 **para la severidad de la depresión, la respuesta al tratamiento,**
8 **la discapacidad y la Calidad de Vida del Estudio TRAL**
9 **multicéntrico y observacional.**

10

11 **Short Title: Prospective follow-up of TRD patients in Mexico**

12 **Título corto: Seguimiento prospectivo de pacientes con TRD en**
13 **México**

14

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Abstract

Introduction: Based on TRAL Mexico subsample, clinical outcomes and Patient-Reported Outcomes (PROs) are reported here. Methods: From 697 patients with MDD recruited from 14 Mexican sites, 140 patients with diagnosis of TRD under standard of care (SOC) were included in the 1-year follow-up. Patients with relevant psychiatric comorbidities or active participation in a clinical trial were excluded. Outcomes were obtained from PROs and clinical assessment scales. Results: Patients were mostly female (82.6%), with a mean age of 47.6 years. Only 44.3% of the patients achieved a clinical response, and remission was around 37% (measured through MADRS). Results from PHQ-9, EQ-5D and SDS show significant symptoms and disability for TRD patients in their everyday life after 1-year of follow-up with SOC. Discussion: TRD patients showed a significant burden of the disease, as current SOC fails to deliver clinically meaningful results for the majority of the patients. Response, remission and relapse are far from the desired outcomes Conclusion: Mexico has undertaken relevant and meaningful strategies to improve mental health resources availability, but some unmet needs are yet to be addressed. All involved stakeholders should consider public policies to enhance clinical outcomes and availability of resources.

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39

40 Key-words: Mexico, Clinical Outcomes, Treatment-Resistant

41 Depressive Disorder, response, Patient-reported outcomes.

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45 Resumen

46 Objetivo: De acuerdo con la submuestra de TRAL de México, estos
47 son los resultados clínicos y los resultados reportados por el
48 paciente (PRO). Material y métodos: De 697 pacientes con TDM
49 reclutados en 14 centros de México, se incluyeron 140 con
50 diagnóstico de DRT con el estándar de atención (SOC) en el
51 seguimiento a 1 año. Se excluyó a pacientes con otros trastornos
52 psiquiátricas relevantes o participación activa en un ensayo
53 clínico. Los resultados se obtuvieron de los PRO y escalas de
54 evaluación clínica. Resultados: En su mayoría, los pacientes
55 fueron mujeres (82.6 %), con edad media de 47.6 años. Solo en
56 44.3 % de los pacientes se logró respuesta clínica y la remisión
57 cercana a 37 % (medida con la MADRS). Los resultados de PHQ-9,
58 EQ-5D y SDS muestran síntomas significativos y discapacidad en
59 pacientes con DRT en su vida diaria después de 1 año de
60 seguimiento con el SOC. Discusión: Los pacientes con DRT
61 tuvieron carga significativa de enfermedad, ya que el SOC actual
62 no brinda resultados clínicamente significativos en la mayoría
63 de los pacientes. La respuesta, remisión y recidiva están lejos
64 de los resultados deseados. Conclusión: Aunque México ha
65 emprendido estrategias relevantes y significativas para mejorar
66 los recursos de salud mental, todavía hay que abordar
67 necesidades insatisfechas. Todas las partes interesadas deben

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considerar políticas públicas para mejorar los resultados clínicos y disponibilidad de recursos.

Palabras clave: México, resultados clínicos, trastorno depresivo resistente al tratamiento, respuesta, resultados reportados por el paciente.

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76 **Background**

77 Major depressive disorder (MDD) is a mental disorder from the
78 depressive spectrum and arguably the most disabling disease
79 worldwide[1]. Beyond the significant global prevalence, this
80 condition poses a challenge to modern societies as it impacts
81 most dimensions of everyday living [2,3]. Although prevalence
82 varies significantly, Latin America (LatAm) seems to be
83 particularly affected by the condition. Previous research showed
84 that Mexico presents lower prevalence values (around 8%)
85 compared to other countries in the region[4].

86 A major concern with MDD is the development of Treatment
87 Resistant depression (TRD). TRD can be defined as a failure to
88 respond to two or more antidepressants at therapeutic doses,
89 over an appropriate period of time, within the current
90 depressive episode[5] -although definition remains as a current
91 discussion topic- which also impacts comparability between
92 countries and regions, as well as an increase in the time to
93 diagnosis. It is estimated that TRD develops in 20-30% of MDD
94 patients and response is rarely over 70% with current Standard
95 of Care (SOC) [6–8]. Treatment is the most pressing issue in TRD.
96 Strategies such as combination, potentiation and augmentation
97 with available therapeutic solutions - ranging from
98 pharmacotherapy to psychotherapy - fail to deliver an adequate

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99 clinical outcome in both response, remission and as prevention
100 for relapse [9–11]. The need for more effective treatment is
101 critical as suicidality is a common outcome of TRD, with
102 increased mortality compared to MDD[12]. The proportion of TRD
103 patients with partial or no response to treatment has been
104 highlighted, although values vary significantly depending on the
105 assessment criteria[13,14].
106 The burden of both MDD and TRD is significant. The impact of the
107 disease goes far beyond the economic and healthcare resource
108 utilization [6,15–17]. Although MDD is a source of obvious burden,
109 this tends to increase significantly in patients developing TRD
110 [6,16,17]. The detrimental effect on daily living has been associated
111 also with humanistic, quality of life (QoL), work-productivity
112 and overall psychosocial dimensions. In this regard, QoL is
113 significantly affected, which is associated with the significant
114 impairment posed by high levels of disability derived by the
115 severe clinical presentation of the disease[18,19].
116 The TRAL (Treatment Resistant Depression in America Latina) was
117 intended to add to the existing literature in the region in
118 which TRD epidemiological data was lacking. This was a
119 multinational, real-world study aiming to estimate the
120 prevalence of TRD among MDD on follow-up at reference centers in

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121 the region. The study provided updates on prevalence of TRD,
122 which was around 30% in MDD patients.
123 This paper presents the results obtained from the subset of
124 Mexico in the phase 2 of the TRAL study, a 1-year follow-up of
125 TRD patients under SOC.
126

127 **Objectives**

128 This study has two main objectives:

129 - To depict a 1-year follow-up of TRD patients in Mexico
130 under Standard-of-care, focused on the characterization of
131 clinical outcomes (depression severity, clinical response,
132 remission and relapse;
133 - To present the PROs (QoL, disability) for 1-year follow-up
134 of TRD patients in Mexico under Standard-of-care providing
135 key indicators of the burden of the disease.

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136 **METHODS**

137 *Study design and population*

138 TRAL was a multicenter, multinational, observational study
139 conducted in a real-world setting (October 2017 - December 2018)
140 based on reference psychiatric sites from 4 countries (Argentina,
141 Brazil, Colombia and Mexico). The main purpose of the TRAL's phase
142 1 was a cross-sectional analysis to portray the epidemiology and
143 disease characterization of TRD in a sample of MDD patients, which
144 constituted the study baseline. Following this, a phase 2 is an 1-
145 year follow-up of TRD patients under SOC for the determination of
146 clinical -depression and suicidality- and safety outcomes, as well
147 as PROs (e.g. work impairment, quality of life, disability). The
148 present analysis depicts the phase 2 data from Mexico, based on a
149 subsample obtained in the country from 13 reference centers (7
150 public and 6 private sites) providing a broad characterization of
151 the whole country. A full list of sites can be found in previous
152 publications[20].

153 Patients that were clinically diagnosed with TRD based on both
154 DSM-5 criteria and MINI, and fulfilling the study's TRD definition,
155 were included in the phase 2 (longitudinal) of the study.

156

157 *Data and assessments*

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158 TRD diagnosis was established based on the criteria defined by
159 protocol. Patients had to be followed up adequately and treated
160 with ≥2 antidepressants -at adequate dose and for adequate
161 duration- in the current episode, with an absence of clinical
162 response to treatment based on MADRS [5]. Validated instruments were
163 used for clinical response and Patient Reported Outcomes.
164 Depression severity was assessed with the Montgomery - Åsberg
165 Depression Rating Scale (MADRS) [21], which shows a good
166 discrimination between responders and non-responders to
167 antidepressants, particularly to assess response to SOC over a 1-
168 year time span (more information can be found here)[20].
169 The Patient Health Questionnaire (PHQ-9), a 10-item questionnaire
170 that characterizes the severity of symptoms on a 4 point scale
171 relative to a pre-defined time frame, usually the last 2 weeks,
172 was also included to assess depression severity [22,23].
173 Sheehan Disability Scale (SDS) was used to assess functional
174 disability from TRD [24]. A patient that scores 5 or more in any of
175 the SDS scales should be closely monitored since it implies
176 significant functional impairment.
177 Quality of life was assessed with the EQ-5D-5L questionnaire [25], a
178 5-dimension questionnaire (Mobility, Self-Care, Usual Activities,
179 Pain/Discomfort, Anxiety/Depression) which also comprises a global
180 assessment visual analogue 100-point scale. Score were also

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converted to the EQ-5D-3L score using responses in the EQ-5D-5L index values based on US values set[26].

Sociodemographic (age, sex, marital status and years of education) and clinical features at baseline were collected (age, depression duration and comorbidities) and assessed by a physician, while clinical features were again collected at the end of the study.

Written informed consent was obtained from all participants. The study was approved by local Independent Ethics Committee / Institutional Review Board.

Statistical Analysis

From the initial Mexican sample of 699 MDD included in phase 1, 140 were included in the phase 2 as per the study criteria – diagnosis of TRD and follow-up. Although the sample size is relevant for Mexico, the study was not designed to be representative for each country, but only for the whole region (LatAm). Therefore, inferences should be performed with care.

Quantitative variables were summarized as mean, median, standard deviation minimum and maximum, and qualitative variables were summarized as absolute frequency and percentages. Longitudinal comparisons on clinical outcomes were performed with a Generalized estimating equation (GEE) for a 95% Confidence interval. There were no multiple testing corrections performed.

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204 There was no imputation of missing data. Statistical significance
205 was set at 5%. Statistical analysis was performed using SAS®
206 (version 9.4, SAS Institute Inc, Cary).
207
208 **RESULTS**
209 **Patient disposition and sociodemographic characteristics over a 1-**
210 **year follow-up with SOC for the Mexican subset**
211
212 From an overall sample of 699 patients with MDD in Mexico,
213 roughly 20% (n=140) were included in phase 2 with a clinical
214 diagnosis of TRD (table 1). Most of these patients (87.1%)
215 completed the study as planned in the protocol and, for those
216 that did not complete (n=18, 12.9%) the main reason was lost to
217 follow up (n=12, 66.7%).
218 Most of the sample identified in phase 1 as having TRD were
219 female patients (82.6%), averaging 47.6 years, with more than
220 half (50.7%) married or on consensual union and 33.1% single.
221 Around 40% had at least 13 years of formal education (table 1).
222
223 **Clinical outcomes of depression and depression severity in TRD**
224 **patients over a 1-year follow-up with SOC for the Mexican subset**
225 *Montgomery-Asberg Depression Scale (MADRS) in TRD patients over a*
226 *1-year follow-up with SOC for the Mexican subset*

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228 The average MADRS score at visit 1 was 30.17 (range: 9 to 50) -
229 Table 2. MADRS total score varied significantly over time
230 ($p<0.0001$), with a mean monthly variation of 1.1 points (B=-
231 1.054)).
232 Almost 27% of the TRD sample had severe depression at visit 1,
233 while at the end of study 10.7% of the patients still presented
234 values consisted with severe depression, with moderate depression
235 representing around 22.1% of the patients. At the end of study
236 visit, 84.3% of the patients still displayed some degree of
237 depressive symptoms.
238 Less than half (44.3%) of the patients showed a clinically
239 significant response (reduction ≥ 50% in the MADRS total score) at
240 the end of the study visit. As for clinically diagnosed relapse,
241 less than 0.8% of the TRD sample showed values in MADRS consistent
242 with these outcome at the end of study visit after 1-year of SOC,
243 while remission was achieved by less than 37% of the patients
244 (table 2).
245

246 *Questionnaire On Patient's Health (PHQ-9) in TRD patients over a*
247 *1-year follow-up with SOC for the Mexican subset*
248

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249 The mean total score of PHQ-9 at visit 1 was 17.01 in TRD patients
250 and more than two-thirds (66.7%) of TRD patients had a moderately
251 severe or severe depression). At the end of study the mean score
252 of phase 2 patients (TRD patients) was 10.3 points and 34.5% of
253 patients had their depression classified as moderately severe or
254 severe (table 3). Moreover, at the end of study, 77.9% of the
255 patients reported having some difficulties conducting their
256 instrumental daily activities.
257

258 **Quality of life (EQ-5D-5L questionnaire) and Disability (Sheehan**
259 **Disability Scale - SDS) in TRD patients over a 1-year follow-up**
260 **with SOC for the Mexican subset**

261 *Quality of Life – EQ-5D-5L Questionnaire in TRD patients over a 1-*
262 *year follow-up with SOC for the Mexican subset*
263 Results from quality of Life can be seen in table 4 as assessed
264 with EQ-5D. At baseline, 54.9% of the patients reported having
265 no problems walking, 48.6% reported having no problems washing
266 or dressing themselves, 18.8% of the patients revealed no
267 problems doing their usual activities, 27.8% of the patients
268 reported having no pain or discomfort and 3.5% of the TRD
269 patients did not feel anxious or depressed. TRD patients seem to
270 have a positive evolution in most dimension at the end of the

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271 study. However, 33.6% of the patients still reported mobility
272 issues, 31.1% had issues with self-care, 50.8% have problems
273 with their usual activities, 54.9% still presented some
274 pain/discomfort and, most importantly, 73.8% still had some
275 anxiety/depression issues.
276 The mean classification of the overall health for TRD patients
277 was 52.9 points at visit 1 and 73.3 points at the end of study,
278 a statistically significant result ($p<0.0001$).
279

280 *Sheehan Disability Scale (SDS) in TRD patients over a 1-year*
281 *follow-up with SOC for the Mexican subset*
282 Table 5 depicts the evolution of values of disability assessed
283 by SDS over 1 year. At visit 1, 6.4% of TRD patients reported
284 that symptoms extremely disrupted their work/school, 6.3% that
285 symptoms extremely disrupted their social life/leisure
286 activities and for 6.9% the symptoms extremely disrupted their
287 family life/home responsibilities. Interestingly, the proportion
288 of patients at the end of study visit varied slightly in most
289 dimensions. Very relevant is the proportion of patients that
290 still reported disruption of work/school activities (87.3%), as
291 well as the 85.2% that still disruption in their social
292 life/leisure activities, and the 87.7 that feel it has disrupted
293 their family/home responsibilities.

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294 The mean total SDS score varied significantly from baseline to
295 the end of study (p<0.0001). On average, TRD patients identify
296 that in at least one day in the past 7 days, the condition has
297 impaired in a significant way from performing at school/work or
298 even missing on their responsibilities.

299

300 **DISCUSSION**

301 This paper follows epidemiological data regarding TRD in
302 Mexico[27]. Within the scope of the TRAL study, Mexico had a
303 significant prevalence of TRD including all patients (20.7%) and
304 only treated patients (23.5%), in line with a high proportion of
305 female patients -over 82%. The present results show that despite
306 the baseline of patients in Mexico -the clinical presentation of
307 the patients seems to be less severe than expected- a
308 significant proportion of the patients do not achieve a clinical
309 response. From a total of around 44% that showed response,
310 almost 37% can be characterized as remitters -contrasting also
311 with the less than 1% of patients with relapse- as assessed with
312 MADRS. Regardless of the outcome, which should be interpreted
313 with caution since sample size was not calculated to allow
314 inferences at a country level, this is still far from desired
315 outcomes. The analysis of other measures of depression severity,

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316 such as PHQ-9, support the evidence that current results
317 achieved with SOC are insufficient. Only about 22% of the
318 patients reported having no difficulties in their everyday life,
319 underscoring the unmet needs in the country and region[20]. The
320 limited access to mental healthcare services in Mexico may offer
321 some explanation to the results, as the reference centers may be
322 confronted with the need to follow patients that are treatment
323 compliant and willing to participate in a study with 5
324 longitudinal assessments. Many TRD patients have economic
325 problems, maybe derived from depression among other causes,
326 leading to problems with long follow-ups in Mexico. Also, Mexico
327 has mixed -public and private sector- mental healthcare offer
328 which were evenly included in this study, contrasting somewhat
329 to what is the reality in other countries.
330 The burden of TRD affects patients in multiple dimensions. The
331 current results show that the assessments based on QoL and
332 disability highlight the need for better outcomes in these
333 dimensions based on the available SOC. The proportion of
334 patients that report on the severe impact of the condition on a
335 daily basis, hindering their independence and adding to the
336 burden of the disease, is high. However, these results are
337 aligned with the vast body of literature available on the
338 subject [6,16-18,28,29]. Considering suicidality, this leads to higher

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339 number of hospitalizations, with increased cost and healthcare
340 resources utilization. On the other hand, school/work
341 productivity is limited which impacts also on families and
342 formal and informal caregivers. This impairment is highlighted
343 in the prevalence of depression and anxiety symptoms after 1-
344 year, which underlines the simultaneous nature of depression and
345 anxiety in these patients [30,31].
346 A significant effort in Mexico has been put in place in the last
347 decade to increase offer in both treatment options and mental
348 health specialists, but there is still some way to go as far as
349 treatment gap [32,33]. This changing trend in the healthcare
350 ecosystem saw improvements in three key areas - prevention,
351 hospitalization and social reintegration- but more effort should
352 be implemented to ensure that objectives are fulfilled [34], namely
353 increased access to primary care[35]. Working on social stigma and
354 ensuring proper patient education is also paramount to the
355 success of the current strategy [36].
356 The study has some limitations assumed on the study design.
357 Real-world provides a more accurate depiction of the reality in
358 Mexico. However, due to the observational nature of the study
359 some variables were not controlled, and study inclusion criteria
360 may have been impacted by the characteristics of each center in
361 the study. Moreover, only patients already followed at the study

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362 centers were included, which may have left some more severe
363 cases out of the study sample. The high proportion of female
364 patients, although expected based on the literature, may impact
365 the overall results, as women tend to have a higher treatment
366 adherence than men[37,38]. Concomitantly, sample size was not
367 designed for inferential analysis and generalization at country
368 level, so data interpretation should be performed with caution.
369 Therefore, this is not a population-based study, as only adults
370 under regular follow-up at medical centers and with a clinical
371 diagnosis of MDD were included in the study.
372 On the other hand, the depiction of the reality in Mexico is
373 enhanced using real-world evidence, and all procedures were put
374 in place to ensure the maximum level of rigor in the study.
375 Regarding this, it is important to mention the inclusion of a
376 diversity of refence centers with different size, expertise and
377 location -including both private and public sites-, as well as
378 the diversity of patient profile and treatment protocols used.
379 Therefore, the present data constitutes a very important
380 reference data source for future decisions in the healthcare
381 context in Mexico, namely in addressing the current medical and
382 societal unmet needs for TRD patients. This is the first study
383 in Mexico on TRD. On a broader perspective, this study adds to
384 the evidence in support of the development of new treatment

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385 protocols for TRD. Also, it is essential to ensure a timely
386 diagnosis and swift medication switch when needed, to avoid the
387 development of more complex and chronic clinical presentations.
388 More psychiatrists are needed in Mexico, as well as a more
389 balanced distribution of healthcare resources -namely the
390 availability of therapeutics in all regions-, suggesting that
391 more investment in mental health is needed.
392
393 *Further research*
394 Future research on the subject should provide a comparative
395 approach to different therapeutics available in Mexico, not only
396 focused on clinical outcomes but also on treatment adherence,
397 patient reported outcomes and other unmet needs in the context
398 of mental healthcare for TRD patients in Mexico. Also of
399 interest is the possibility of performing sub-group analysis
400 that allow the identification of factors associated with good
401 prognosis, as well as to understand the subtleties of the
402 variation in values for the PRO based on patients achieving
403 response/non-response to treatment.
404
405 **CONCLUSIONS**
406 The burden of TRD in LatAm is significant. Available clinical
407 protocols based on standard of care do not provide the necessary

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408 clinical outcomes for those in need. Due to the life-

409 threatening nature of TRD, associated with high levels of

410 suicidality, a urgent call to action is necessary which includes

411 all relevant stakeholders and decision makers in Mexico to

412 ensure proper measures are enforced. The action plan should also

413 consider that the burden of disease strains the already limited

414 healthcare resources on mental health existent in the country,

415 as well as caregivers and patients alike. Effort should also be

416 placed on achieving a scientific consensus on the definition of

417 TRD that leads to an easier operationalization of screening,

418 diagnosis and treatment. Results from the TRAL study have the

419 potential to become a relevant decision-making supporting tool

420 to ensure adequate decisions and aid for those in need in

421 Mexico.

422

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523 **Table 1. Patient disposition and Sociodemographic data at visit**

524 **1 (baseline) in the Mexican subset**

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	TRD (n=144)
Age (years)	
N	144
Mean	47.60
Median	47.50
Standard deviation	12.98
Minimum	18.00
Maximum	80.00
Gender, n (%)	
Female	119 (82.6%)
Male	25 (17.4%)
Total	144
Marital status, n (%)	
Single	47 (33.1%)
Married/Consensual Union	72 (50.7%)

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	TRD (n=144)
Divorced/Separated	16 (11.3%)
Widower	7 (4.9%)
Total	142
Years of formal education, n (%)	
0	0
1-4 years	0
5-9 years	42 (29.6%)
10-12 years	43 (30.3%)
≥ 13 years	57 (40.1%)
Total	142
Analysis dataset for phase 2 by visit, n (%)	
Visit 1	140 (100.0%)

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	TRD (n=144)
Visit 2	132 (94.3%)
Visit 3	124 (88.6%)
Visit 4	122 (87.1%)
Visit 5 (end of study)	122 (87.1%)
For patients enrolled in the phase 2	
Patient completed the study as planned into the protocol, n (%)	
No	18 (12.9%)
Yes	122 (87.1%)
Total	140

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	TRD (n=144)
If no, reason for premature withdrawal, n (%)	
The subject withdraws his consent	2 (11.1%)
The subject is lost to follow up	12 (66.7%)
The subject died	2 (11.1%)
Other reason	2 (11.1%)
Total	18

525 MDD - Major Depressive Disorder. TRD - Treatment Resistant
526 Depression.

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527

528 **Table 2. Montgomery-Asberg Depression Scale (MADRS) in TRD**
529 **patients over a 1-year follow-up with SOC for the Mexican subset**

	Visit 1 (n=144)	Visit 2 (n=132)	Visit 3 (n=124)	Visit 4 (n=122)	End of study* (n=122)
Total score[a)]					
N	144	132	124	122	122
Mean	30.17	22.16	20.19	19.51	17.64
Standard	8.63	11.16	11.20	11.21	11.87
Minimum	9.00	0.00	0.00	0.00	0.00
Maximum	50.00	45.00	48.00	45.00	48.00
GEE model	50.00	48.00	46.00	49.00	47.00
B (linear			-1.054		
95% CI			[-1.222; -0.885]		
p-value			<0.0001		
Symptom absent	0	14	14	16	19
Mild depression	21	38	48	50	63
Moderate (20-34)	77	54	44	40	27
Symptom	98	106	106	106	109
Severe depression	46	26	18	16	13
Change in total score from visit 1 (%)					
N		132	124	122	122
Mean		-25.58	-31.04	-32.53	-39.92
Standard		31.66	34.73	35.92	36.87
Minimum		-100.00	-100.00	-100.00	-100.00
Maximum		75.00	100.00	87.50	100.00
Response (Reduction ≥50% in the total					
Yes		24	32	38	54
Total		132	124	122	122
Remission (MADRS total score ≤12), n					
Yes		28	27	31	45
Total		132	124	122	122
Relapse, n (%)					
Yes			6 (4.8%)	5 (4.1%)	1 (0.8%)

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	Visit 1 (n=144)	Visit 2 (n=132)	Visit 3 (n=124)	Visit 4 (n=122)	End of study* (n=122)
Total			124	122	122

TRD - Treatment Resistant Depression. GEE: Generalized estimating equation. 95%CI: 95% Confidence interval.

a) Range: 0 to 60. Higher values indicate a higher level of depression. *End of study – final visit, after 1 year follow-up

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532 **Table 3. Reported analysis of Questionnaire on Patient's Health**

533 **(PHQ-9) of TRD patients over a 1-year follow-up with SOC for the**

534 **Mexican subset**

535

	Visit 1 (n=144)	**Visit 3 (n=124)**	**End of study (n=122)**	**Longitudinal analysis** GEE model	
Total score[a)]					
N	144	124	122		
Mean	17.01	12.06	10.28		
Median	17.00	11.50	8.00	B (linear regression parameter)	-0.556
Standard deviation	5.49	7.02	7.80	95% CI	[-0.664; -0.447]
Minimum	2.00	0.00	0.00	p-value	<0.0001
Maximum	27.00	27.00	27.00		
Depression severity, n (%)					
None (0-4)	2 (1.4%)	20 (16.1%)	39 (32.0%)		

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	Visit 1 (n=144)	Visit 3 (n=124)	End of study (n=122)	Longitudinal analysis GEE model
Mild (5-9)	10 (6.9%)	28 (22.6%)	28 (23.0%)	
Moderate (10-14)	36 (25.0%)	25 (20.2%)	13 (10.7%)	
Moderately severe (15-19)	42 (29.2%)	25 (20.2%)	24 (19.7%)	
Severe (20-27)	54 (37.5%)	26 (21.0%)	18 (14.8%)	
Total	144	124	122	
If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?, n (%)				
Not difficult at all	4 (2.8%)	18 (14.5%)	27 (22.1%)	

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	Visit 1 (n=144)	Visit 3 (n=124)	End of study (n=122)	Longitudinal analysis GEE model
Somewhat difficult	56 (38.9%)	74 (59.7%)	77 (63.1%)	
Very difficult	65 (45.1%)	31 (25.0%)	16 (13.1%)	
Extremely difficult	19 (13.2%)	1 (0.8%)	2 (1.6%)	
Total	144	124	122	

536 a) Total score range between 0 and 27 and higher values indicate
537 higher depression severity.
538 MDD - Major Depressive Disorder. TRD - Treatment Resistant
539 Depression. GEE: Generalized estimating equation. 95%CI: 95%
540 Confidence interval.
541

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542 **Table 4. Quality of life - EQ-5D-5L questionnaire over a 1-year**

543 **follow-up of TRD patients with SOC for the Mexican subset**

	Visit 1 (n=144)	**End of study (n=122)**	**Longitudinal analysis** GEE model
Mobility, n (%)			
I have no problems walking	79 (54.9%)	81 (66.4%)	
I have slight problems walking	26 (18.1%)	22 (18.0%)	
I have moderate problems walking	35 (24.3%)	18 (14.8%)	
I have severe problems walking	3 (2.1%)	1 (0.8%)	
I am unable to walk	1 (0.7%)	0	
Total	144	122	
Self-care, n (%)			
I have no problems washing or dressing myself	70 (48.6%)	84 (68.9%)	

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	Visit 1 (n=144)	End of study (n=122)	Longitudinal analysis GEE model
I have slight problems washing or dressing myself	27 (18.8%)	20 (16.4%)	
I have moderate problems washing or dressing myself	35 (24.3%)	17 (13.9%)	
I have severe problems washing or dressing myself	12 (8.3%)	1 (0.8%)	
I am unable to wash or dress myself	0	0	
Total	144	122	
Usual activities, n (%)			
I have no problems doing my usual activities	27 (18.8%)	60 (49.2%)	

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	Visit 1 (n=144)	End of study (n=122)	Longitudinal analysis GEE model
I have slight problems doing my usual activities	38 (26.4%)	31 (25.4%)	
I have moderate problems doing my usual activities	57 (39.6%)	28 (23.0%)	
I have severe problems doing my usual activities	18 (12.5%)	3 (2.5%)	
I am unable to do my usual activities	4 (2.8%)	0	
Total	144	122	
Pain/discomfort, n (%)			
I have no pain or discomfort	40 (27.8%)	55 (45.1%)	
I have slight pain or discomfort	36 (25.0%)	38 (31.1%)	

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	Visit 1 (n=144)	End of study (n=122)	Longitudinal analysis GEE model
I have moderate pain or discomfort	44 (30.6%)	24 (19.7%)	
I have severe pain or discomfort	19 (13.2%)	3 (2.5%)	
I have extreme pain or discomfort	5 (3.5%)	2 (1.6%)	
Total	144	122	
Anxiety/depression, n (%)			
I am not anxious or depressed	5 (3.5%)	32 (26.2%)	
I am slightly anxious or depressed	25 (17.4%)	55 (45.1%)	
I am moderately anxious or depressed	59 (41.0%)	25 (20.5%)	
I am severely anxious or depressed	42 (29.2%)	7 (5.7%)	

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	Visit 1 (n=144)	**End of study (n=122)**	**Longitudinal analysis** GEE model	
I am extremely anxious or depressed	13 (9.0%)	3 (2.5%)		
Total	144	122		
Health in the current day[a)]				
N	144	122		
Mean	52.90	73.32		
Median	51.50	80.00	B (linear regression parameter)	0.801
Standard deviation	19.56	19.21	95% CI	[0.395; 1.207]
Minimum	0.00	20.00	p-value	0.0001
Maximum	90.00	100.00		
EQ-5D-3L score[b)]				
N	144	122		
Mean	0.64	0.79		

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	Visit 1 (n=144)	End of study (n=122)	Longitudinal analysis GEE model	
Median	0.67	0.82	B (linear regression parameter)	0.012
Standard deviation	0.17	0.16	95% CI	[0.009; 0.014]
Minimum	-0.06	0.24	p-value	<0.0001
Maximum	1.00	1.00		
Score recoded as categorical variable, n (%)				
Worst health status (score <0.403)	14 (9.7%)	5 (4.1%)		
Higher health status (score ≥0.403)	130 (90.3%)	117 (95.9%)		
Total	144	122		

a) The health in current day was assessed through a visual analogic scale (range 0=worst health to 100=best health).

b) Score was calculated based on response combinations and using US population/scores as a reference.

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548 MDD - Major Depressive Disorder. TRD - Treatment Resistant

549 Depression. GEE: Generalized estimating equation. 95%CI: 95%

550 Confidence interval.

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552 **Table 5. Sheehan Disability Scale (SDS) over a 1-year follow-up**
553 **of TRD patients with SOC for the Mexican subset**

	Visit 1 (n=144)	**Visit 3 (n=124)**	**End of study (n=122)**	**Longitudinal analysis** GEE model
The symptoms have disrupted your work /school, n (%)				
Not at all	7 (6.4%)	9 (11.5%)	10 (12.7%)	
Mildly	15 (13.6%)	16 (20.5%)	23 (29.1%)	
Moderately	31 (28.2%)	37 (47.4%)	34 (43.0%)	
Markedly	50 (45.5%)	13 (16.7%)	11 (13.9%)	
Extremely	7 (6.4%)	3 (3.8%)	1 (1.3%)	
Total	110	78	79	
N	110	78	79	
Mean	5.91	4.59	4.04	
Median	7.00	5.00	4.00	

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	Visit 1 (n=144)	Visit 3 (n=124)	End of study (n=122)	Longitudinal analysis GEE model
Standard deviation	2.75	2.64	2.48	
Minimum	0.00	0.00	0.00	
Maximum	10.00	10.00	10.00	
The symptoms have disrupted your social life/leisure activities, n (%)				
Not at all	4 (2.8%)	14 (11.3%)	18 (14.8%)	
Mildly	13 (9.0%)	26 (21.0%)	46 (37.7%)	
Moderately	43 (29.9%)	61 (49.2%)	40 (32.8%)	
Markedly	75 (52.1%)	19 (15.3%)	18 (14.8%)	
Extremely	9 (6.3%)	4 (3.2%)	0	
Total	144	124	122	

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	Visit 1 (n=144)	Visit 3 (n=124)	End of study (n=122)	Longitudinal analysis GEE model
N	144	124	122	
Mean	6.45	4.36	3.74	
Median	7.00	4.00	3.00	
Standard deviation	2.29	2.45	2.50	
Minimum	0.00	0.00	0.00	
Maximum	10.00	10.00	9.00	
The symptoms have disrupted your family life/home responsibilities, n (%)				
Not at all	4 (2.8%)	15 (12.1%)	15 (12.3%)	
Mildly	11 (7.6%)	33 (26.6%)	49 (40.2%)	

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	Visit 1 (n=144)	Visit 3 (n=124)	End of study (n=122)	Longitudinal analysis GEE model
Moderately	61 (42.4%)	53 (42.7%)	41 (33.6%)	
Markedly	58 (40.3%)	21 (16.9%)	17 (13.9%)	
Extremely	10 (6.9%)	2 (1.6%)	0	
Total	144	124	122	
N	144	124	122	
Mean	6.24	4.23	3.70	
Median	6.00	4.00	3.00	
Standard deviation	2.23	2.37	2.43	
Minimum	0.00	0.00	0.00	
Maximum	10.00	10.00	9.00	
Total score				
N	110	78	79	
Mean	18.68	13.31	12.28	

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	Visit 1 (n=144)	Visit 3 (n=124)	End of study (n=122)	Longitudinal analysis GEE model	
Median	20.00	15.00	14.00	B (linear regression parameter)	-0.518
Standard deviation	6.56	6.97	7.01	95% CI	[-0.645; -0.390]
Minimum	2.00	0.00	0.00	p-value	<0.0001
Maximum	30.00	30.00	27.00		
On how many days in the past 7 days did your symptoms cause you to miss school or work or leave you unable to carry out your normal daily responsibilities					
N	144	124	122		
Mean	1.72	1.12	1.04		

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	Visit 1 (n=144)	Visit 3 (n=124)	End of study (n=122)	Longitudinal analysis GEE model
Median	1.00	0.00	0.00	
Standard deviation	2.14	1.68	1.65	
Minimum	0.00	0.00	0.00	
Maximum	7.00	7.00	7.00	
On how many days in the past 7 days did you feel so impaired by your symptoms, that even though you went to school or work or had other daily responsibilities, your productivity was reduced				
N	144	124	122	
Mean	2.16	1.52	1.09	

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	Visit 1 (n=144)	Visit 3 (n=124)	End of study (n=122)	Longitudinal analysis GEE model
Median	2.00	1.00	0.00	
Standard deviation	2.04	1.69	1.37	
Minimum	0.00	0.00	0.00	
Maximum	7.00	7.00	5.00	

554 TRD - Treatment Resistant Depression. GEE: Generalized
555 estimating equation. 95%CI: 95% Confidence interval.
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