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ORIGINAL RESEARCH ARTICLE

Cost-Utility Analysis of Esketamine for Patients with Treatment-Resistant Depression in Italy

Carla Rognoni[1] · Camilla Falivena[1] · Francesco Costa[1] · Patrizio Armeni[1]

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Abstract

Aim Major depressive disorder is considered one of the most frequent diseases in the general population, and treatment-resistant depression (TRD) represents the subset with more significant clinical and social impact. Large, robust phase III studies have shown safety and efficacy of esketamine nasal spray plus SSRI/SNRI antidepressants (ADs) compared with SSRI/SNRI plus placebo nasal spray in patients with TRD. The main aim of this study was to perform a cost-utility analysis comparing esketamine plus ADs with ADs alone in TRD patients, from the societal perspective in Italy. A secondary analysis focused on the National Healthcare Service (NHS) perspective.

Methods A Markov multistate model has been developed to estimate quality-adjusted life years and economic outcomes of both treatment strategies over 5 years considering the initiation of esketamine in the different treatment lines, from 3 to 5 (3L–5L). The model has been populated with data from literature and real-world evidence. The analysis from the societal perspective considered direct healthcare costs and patients' productivity losses. In addition to the incremental cost-utility ratio (ICUR), the incremental net monetary benefit (INMB) has been calculated as (incremental benefit × WTP) − incremental cost and by applying a willingness-to-pay (WTP) of 50,000€/QALY. Deterministic and probabilistic sensitivity analyses have been performed to assess the robustness of the model results.

Results From the societal perspective, the ICUR ranged between 16,314€ and 22,133€ per QALY according to the different treatment lines, while it was over the threshold of 100,000€/QALY for the NHS perspective. The INMB was positive and ranged from 2259€ to 2744€ across treatment lines in the societal perspective; the INMB begins to occur earlier when moving towards subsequent lines of treatment (3.9 years for 3L, 3.6 years for 4L and 3.5 years for 5L). The analyses showed also that the advantage in terms of INMB is maintained for a wide range of societal preferences expressed by WTP thresholds, and in particular for values above 22,200€, 16,400€ and 17,100€ for 3L, 4L and 5L, respectively.

Conclusion The study showed that esketamine may be a cost-effective opportunity from the societal perspective for the management of patients with treatment-resistant depression. In the future, data collected from observational studies or registries, which can include the collection of productivity losses and also costs sustained by the patients, will be able to provide further evidence in order to improve the reliability of the model results.

1 Introduction

Depression, affecting globally more than 322 million people of all ages [1], is considered one of the most frequent diseases in the general population and the leading cause of disability worldwide [2]. Depressive disorders are characterized by different symptoms, like sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness, and poor concentration. Depression can be chronic or recurrent, substantially impairing an individual's ability to function at work or school or cope with daily life. At its most severe, depression can lead to suicide [3]. Recent estimates report the lifetime prevalence of major depressive disorder (MDD), in which depressive episodes last typically several months [4], in the range of 2–21% based on different countries, with an average lifetime prevalence of about 5% in the European Union [1]. These patients are subject to high occurrence of comorbid

✉ Carla Rognoni
carla.rognoni@unibocconi.it

[1] Centre for Research on Health and Social Care Management (CERGAS), SDA Bocconi School of Management, Bocconi University, Via Sarfatti 10, 20136 Milan, Italy

Key Points

This study investigated the cost–utility profile of intranasal esketamine plus antidepressants versus antidepressants alone in patients with treatment-resistant depression, from the societal and NHS perspectives in Italy.

A Markov model has been developed to estimate quality-adjusted life years and costs of both treatment strategies over 5 years considering the initiation of esketamine in different treatment lines, from third to fifth (3L–5L).

Considering a willingness-to-pay threshold of 50,000€/QALY, the incremental net monetary benefit of esketamine plus antidepressants, from the societal perspective, was positive and ranged from 2259€ to 2744€ across treatment lines, showing that this treatment strategy may be a cost-effective opportunity for the management of patients with treatment-resistant depression.

physical illness, heavily impacting healthcare services, society and quality of life [5].

Depression is also a highly recurring disorder, as it is reported that more than two-thirds of patients may have recurring episodes and/or relapses; in particular, after a first episode, the probability of a relapse is 50%, while after a second episode the probability of a third exceeds 90% [4]. The primary goal in the treatment of depression is the complete resolution of symptoms such as remission; nevertheless, clinical experience and literature data indicate that, with current treatments, approximately one third of patients with MDD do not respond adequately to them [6, 7].

Treatment-resistant depression (TRD) is defined as lack of clinically meaningful improvement despite the use of adequate doses of at least two antidepressant agents, derived from the group(s) of commonly used first-line treatments, prescribed for an adequate duration with adequate affirmation of treatment adherence [8, 9]. Patients with TRD are at increased risk of relapse, suicide and substance abuse, have more frequent psychiatric and/or physical comorbidities, and suffer from significant and prolonged social, work and interpersonal maladjustment [10, 11]. Resistance to treatment therefore represents a phenomenon of significant clinical and social impact, justifying the growing interest of clinicians and researchers on this issue.

In this context, esketamine (Spravato®, Janssen-Cilag) has been approved by the European Commission for the treatment of TRD [12]. Esketamine is a non-competitive, non-selective antagonist of the N-methyl D-aspartate (NMDA) glutamate receptor, whose administration over time can promote the restoration of brain synaptic connections in patients with TRD, improving mood symptoms [12]. Esketamine is delivered through a single-use nasal spray device that delivers a total of 28 mg, in two sprays (one spray per nostril). In the induction phase, the recommended total dose at each treatment session is 56 mg or 84 mg twice a week (week 1–4), based on the patient's age and response to treatment, using one to three devices administered 5 min apart [12]. In the maintenance phase, the requested dose is 56 mg or 84 mg per week from week 5 to week 8, and 56 mg or 84 mg every week or every 2 weeks from week 9 onwards. Esketamine treatment must be initiated in conjunction with an oral antidepressant regimen from an SSRI or SNRI class.

Large, robust phase III studies have shown short- and long-term safety and efficacy of esketamine nasal spray plus SSRI/SNRI antidepressants (ADs) compared with placebo plus SSRI/SNRI in patients with TRD [13–18].

The aim of the present study was to develop knowledge on the clinical and economic aspects that can support stakeholders at the national level in Italy in the overall assessment of choices regarding the management of patients with TRD. In particular, the main aim of the study was to perform a cost-effectiveness analysis comparing esketamine plus ADs with ADs alone in TRD patients, from the societal perspective in Italy. A secondary aim of the study was to consider the NHS perspective for the analyses.

2 Methods

A cost-utility analysis (CUA) has been developed to project costs and QALYs associated with esketamine plus ADs versus ADs in the population considered from the societal perspective in Italy. In addition to the classical representation of cost-effectiveness results, the considered treatment strategies have been compared through the summary metric of incremental net monetary benefit (INMB), which is the difference between the benefits and the costs of each treatment (expressed in monetary units). The broader societal perspective allows the inclusion of tangible and intangible returns for the patients with TRD. Monetary valuations of benefits are commonly obtained through the application of a willingness-to-pay (WTP) threshold. Overall, the analysis is a rational approach for economic evaluations, consistent with the 'value-based healthcare' paradigm [19] which is now emerging as the future methodology to decision making.

The analysis was reported according to Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [20, 21]. The CHEERS checklist is reported in the electronic supplementary material (ESM, Appendix 1).

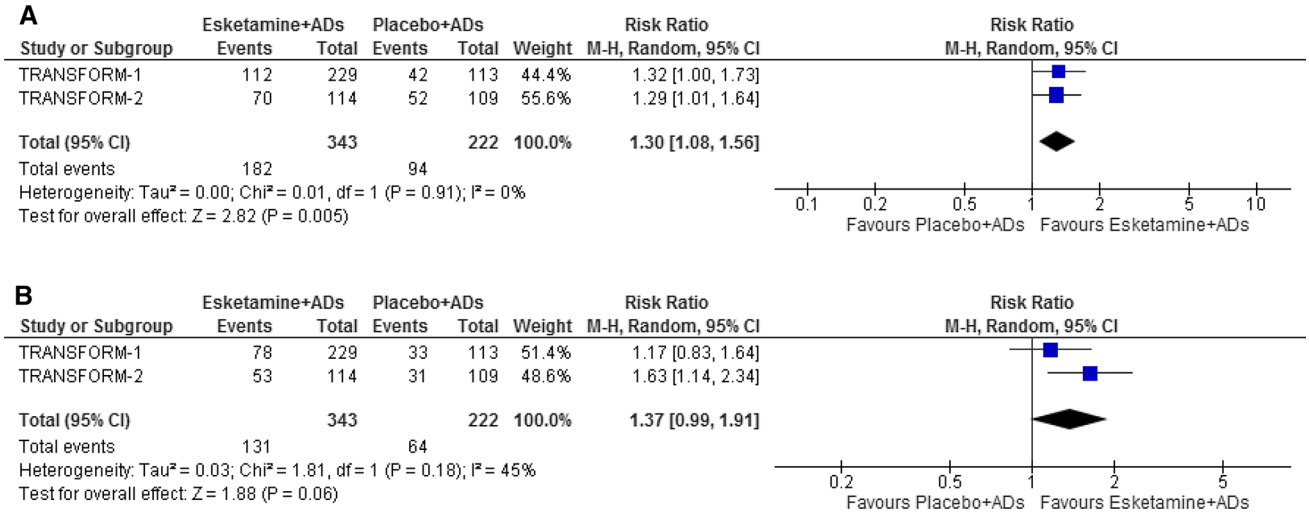


Fig. 1 Clinical response (**A**) and clinical remission (**B**) of esketamine plus antidepressants (ADs) versus placebo plus ADs: meta-analysis of TRANSFORM-1 and TRANSFORM-2 studies

2.1 Clinical Data Synthesis

We conducted a random effect meta-analysis on clinical response and clinical remission considering data from TRANSFORM-1 [13] and TRANSFORM-2 [14] studies, pooling the two esketamine doses in TRANSFORM-1 (56 mg and 84 mg) into one single esketamine arm. We considered these trials because they were homogenous in terms of inclusion and exclusion criteria, study design, and outcomes. In particular, in TRANSFORM-1, eligible patients ($N=346$) were randomized (1:1:1) to twice-weekly nasal spray treatment (esketamine [56 or 84 mg] or placebo), while in TRANSFORM-2, patients ($N=223$) were randomly assigned to treatment with esketamine nasal spray (56 or 84 mg twice weekly) and an antidepressant or antidepressant and placebo nasal spray. Eligible patients were between 18 and 64 years of age with recurrent MDD or single-episode MDD (≥ 2 years), without psychotic features, confirmed by the Mini-International Neuropsychiatric Interview. Patients' mean age was similar in the two studies (47 years for TRANSFORM-1 and 46 years for TRANSFORM-2). In both studies, clinical response was defined as at least 50% improvement in MADRS (Montgomery-Åsberg Depression Rating Scale) [22] at week 4 from baseline, while clinical remission was defined as reaching ≤ 12 on the MADRS scale at week 4. A follow-up of 24 weeks was considered for both studies. Meta-analyses forest plots are reported in Fig. 1 in terms of relative risks (RR).

Meta-analysis of the two trials showed that patients on esketamine plus background antidepressant were more likely to achieve a clinical response compared with placebo plus antidepressant (RR 1.30; 95% CI 1.08–1.56) (Fig. 1A), while the relative likelihood of clinical remission was higher with esketamine with a borderline statistical significance (RR 1.37; 95% CI 0.99–1.91) (Fig. 1B).

2.2 The Model

A Markov multistate model, which enables representation of the possible clinical pathways, has been developed to estimate quality-adjusted life years (QALYs) and economic outcomes associated with esketamine plus ADs versus ADs alone in patients with TRD. The model has been built with TreeAge Pro software (Williamstown, MA, USA). The development started with the identification of the main health states for TRD patients according to a search in the literature [23, 24]. The health states considered in the model were 'initiation treatment', 'remission', 'response', 'relapse' and 'no response'. Initiation refers to the initial treatment period of 4 weeks; remission consists of a complete resolution of symptoms (≤ 12 on MADRS scale) while response is a partial resolution of depressive symptoms (at least 50% improvement in MADRS); relapse is recurrence of symptoms after initial response or remission and no response is the failure to achieve response or remission. The model structure is presented in Fig. 2, while Supplementary Fig. 1 (see ESM) reports patients' distributions (Markov cohort analysis) over time among the health states for esketamine plus ADs and ADs alone.

The model takes into account overall mortality according to Italian life tables [25]. Because the literature reports an increased risk of death (RR 1.52, 95% CI 1.45–1.59) compared with the general population for patients with depression [26], this risk has been considered in the model. In order to simplify the representation, all-cause mortality

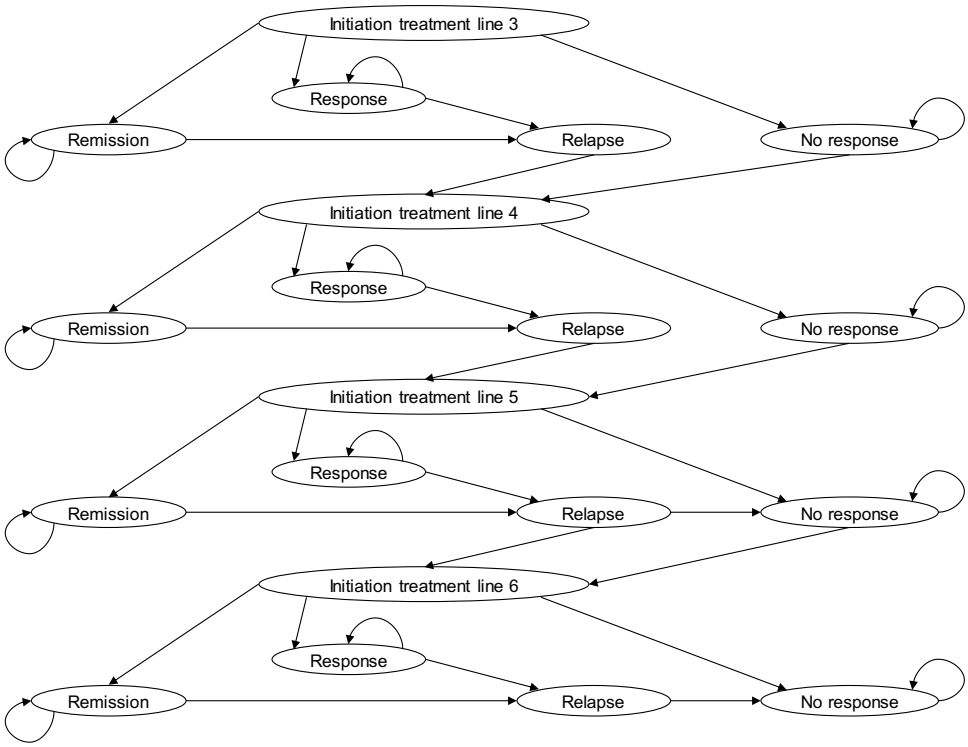


Fig. 2 Markov model representation

transitions (which apply to all health states) are not reported in Fig. 2.

The setting of the analysis was the failure of at least two AD treatments, and real-world data [27] were used to populate the model with a hypothetical cohort of patients with TRD, with mean age of 51 years and 62.3% females. Different analyses have been performed considering the number of AD treatments failed, from 2 to 4 [27].

Patients eligible for third-line treatment enter a Markov model in the 'initiation treatment line 3' health state; patients with effective response to treatment move to the 'response' state, while patients with depression remission move to the 'remission' state. Patients with inadequate response (no response) move to a subsequent line of therapy (alternative antidepressants). In case of relapse, patients will move from 'response' or 'remission' to the 'relapse' health state. Patients with no response to a given treatment will receive it for 8 weeks (4 weeks in initiation, 4 weeks in non-response), according to recommendations published in the literature [28, 29]. Patients eligible for fourth-line treatment enter the model in the 'initiation treatment line 4' health state, while patients eligible for fifth-line treatment enter the model in the 'initiation treatment line 5' health state and so on for the sixth line. The model considers up to six treatment lines due to the lack of efficacy data on longer clinical pathways. For patients reaching the sixth line of treatment, the distribution among the different health states after the therapy is maintained over time since no other treatments are considered.

For ADs strategy, rates of remission, response and relapse were retrieved from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial [6], in which outpatients with MDD were followed across four treatment lines. The trial reported for third-line treatment that 13.7% and 16.8% of patients were in remission or response, respectively, after about 6 weeks. For the fourth-line treatment, these values were 13% and 16.3%, respectively. The mean time to reach remission or response was about 7 and 8 weeks, respectively. Due to the lack of specific data, for the fifth and six lines of treatment we referred to the values of the fourth line. In order to transform these probabilities on a weekly basis, and to include them in the model, we referred to transformations presented in [30] and we assumed transition probabilities constant over time.

For esketamine plus AD treatment, the model has been informed by clinical response and clinical remission data obtained from the meta-analyses; concerning relapse rates, we made reference to the data published by the SUSTAIN-1 study, which compared the efficacy of esketamine + ADs versus ADs alone in delaying relapse of depressive symptoms in patients in stable remission after a treatment with esketamine + ADs [16]. This study indicates that under continuous esketamine treatment, patients free from relapse are about 58% from 36 weeks (about 9 months) onwards, while patients who stopped esketamine reported free from relapse rates of about 38% from 43 weeks onward. We assumed a maximum treatment duration for esketamine of 9 months for patients in disease remission (scenario A, baseline) as the

summary of product characteristics reports that once depressive symptoms have improved, it is recommended to continue treatment for at least 6 months [12]. After this period, we applied relapse rates from the SUSTAIN-1 study related to patients who stopped esketamine.

As the longest follow-up considered in the studies was about 24 months, a time horizon of 5 years has been considered in the model to guarantee adequate accrual of long-term costs and benefits without requiring extreme extrapolations. A discount rate of 3% has been applied to QALYs and costs [31] and 1-week Markov cycle length has been chosen in order to follow dose adjustments according to the indications of the summary of product characteristics. Model parameters are reported in Table 1.

2.3 Healthcare Resource Consumption and Costs

This analysis was performed primarily from the societal perspective in Italy and both direct healthcare resource consumption (direct costs) and productivity losses were included (€, year 2021).

Costs for the different AD treatment lines and for the healthcare resource utilization for patients with TRD were derived from a retrospective analysis of administrative databases covering about 10% of the Italian population (Veneto region, ASL Bergamo) [32]. For the cost attribution, the price at the time of purchase for drug treatments was considered, while the costs for the hospitalizations were derived directly from DRG codes; outpatient specialist visits costs were derived from regional tariffs.[1] Costs for psychiatric hospitalizations and non-hospital residential facilities (the management of patients in specific territorial centers) have been assumed equal to zero for esketamine for patients in remission or response since the study by Daly and colleagues [16] did not report hospital admissions or access to residential facilities for the management of patients under esketamine in these health states. A summary of mean annual costs per patient according to treatment lines is reported in Table 1.

With regard to esketamine, a cost of 199.50€ has been considered for a single dose (28 mg) (cost provided by the producer). Considering the flexible dose of esketamine in the trials, monthly costs were obtained by the multiplication of the cost of the device, the mean number of administration sessions per month and the mean number of devices per session (Table 1, data collected during TRANSFORM-2 [14] and SUSTAIN-1 [16] trials and provided by the producer). For the first month of treatment (induction) a cost of 3734.95€ has been calculated, while the maintenance phase showed a monthly cost ranging from 2061.98€ (first month of maintenance phase) to 1479.02€ (subsequent months). Since esketamine administration requires observation of the patient after each administration, a physician office visit was assigned for each drug administration [24] (Table 1). We assumed a working time loss of 3 h for the patient for the administration of esketamine according to data already reported in the literature [23].

A longer time horizon study [18] reported that common (involving ≥ 10% of patients) treatment-emergent adverse events (TEAEs) for esketamine were dizziness (32.9%), dissociation (27.6%), nausea (25.1%), headache (24.9%), somnolence (16.7%), dysgeusia (11.8%), hypoesthesia (11.8%), vertigo (11%), vomiting (10.8%) and viral upper respiratory tract infection (10.2%). By pooling the frequencies of these adverse events, the mean number of TEAEs per patient was 1.828. Similar patterns of TEAEs were also reported in studies with shorter time horizons [13, 14]. These studies reported that the majority of TEAEs were mild or moderate in severity and that most of the clinically relevant TEAEs were transient and resolved on the same day of esketamine administration. For these reasons, no decrease in patients' quality of life was applied and the management of the TEAE was assumed to be performed during a psychiatric visit.

With regard to social costs, we performed a systematic literature review in order to retrieve the working days lost by patients with TRD. The search focused on studies conducted in Europe (including Italy). The details of the search strategy are reported in the ESM (Appendix 3). The study by Taipale and colleagues [33] reported 100.1 days lost for TRD in a period of 8 months; a European study reported a working time loss of 57% [27], while another study conducted in Belgium [34] showed an average number of calendar days 'not working' per month of 22.2 during a major depressive episode. A study conducted in Italy [35] reported a mean of 42 working days lost per year for patients with TRD, while a study conducted in the UK showed an overall work impairment of 51% for those patients [36]. The overall average working time lost was 51.40% (SD 20.22%). For the estimation of productivity losses, we applied the human capital approach and assigned a tariff to each working day lost. We considered an average annual salary of 31,252€ (2019

[1] The structures that provide inpatient and outpatient care within the Italian Healthcare Service are financed according to pre-defined tariffs. Ordinary hospital admissions, day hospital and day surgery cases are classified according to the DRG (Diagnosis Related Group) system; DRG tariffs are supposed to cover most hospital costs, including administration costs and overheads. The national DRG tariffs are set equal for all types of providers. The regions are free, however, to adopt changes if they wish to differentiate tariffs among various types of hospitals. Similarly, outpatient tariffs are defined at the national and regional level for healthcare services used in ambulatorial settings.

Table 1 Model parameters and related distributions

Parameter	Base-case value	Distribution	Alpha	Lambda or beta	References
Esketamine efficacy relative to antidepressants (relative risk)		Gamma			TRANSFORM-1 [13] and TRANSFORM-2 [14]
Clinical response	1.30		117.36	90.28	
Clinical remission	1.37		35.48	25.90	
Relative risk of mortality for depressive patients vs general population	1.52	Gamma	1444	950	[26]
Healthcare resource utilization					
No. of esketamine administration sessions per week:		Gamma			TRANSFORM-2 [14] and SUSTAIN-1 [16]
Initiation phase	1.85		25.00	13.51	
Optimization phase (month 2)	0.992		25.00	25.20	
Maintenance phase (month 2+)	0.711		25.00	35.16	
No. of esketamine devices per administration session:		Gamma			TRANSFORM-2 [14] and SUSTAIN-1 [16]
Initiation phase	2.530		25.00	9.88	
Optimization phase (month 2)	2.605		25.00	9.60	
Maintenance phase (month 2+)	2.605		25.00	9.60	
Mean number of adverse events per patient starting esketamine treatment	1.828	Gamma	25.00	13.68	SUSTAIN-2 [18]
Costs					
Esketamine cost (single device 28 mg)	199.50€	Gamma	25.00	0.13	Cost provided by the producer
Esketamine single administration		Gamma			National Healthcare Service price list (code 94.12.1)
Psychiatric visit	12.91€		25.00	1.94	
Administration of therapeutic substances	6.97€		25.00	3.59	National Healthcare Service price list (code 83.98)
Healthcare resource utilization (weekly cost): drugs, visits/exams, other hospitalizations (every health state)		Gamma			[32]
Treatment line 3	72.94€		1823.56	25.00	
Treatment line 4	80.04€		2000.96	25.00	
Treatment line 5+	95.85€		2396.15	25.00	
Residentiality (weekly cost) (every health state)		Gamma			[32]
Treatment line 3	39.04€		975.96	25.00	
Treatment line 4	76.06€		1901.44	25.00	
Treatment line 5+	178.94€		4473.56	25.00	
Psychiatric hospitalizations (weekly cost) (every health state)		Gamma			[32]
Treatment line 3	22.65€		566.35	25.00	
Treatment line 4	45.83€		1145.67	25.00	
Treatment line 5+	61.38€		1534.62	25.00	
Productivity data					
Patients' mean weekly wage	Age 45–54: 602€	Gamma	25	0.042	[37]
	Age 55–67: 646€		25	0.039	
Percent of patients with lost productivity in non-response health state (every treatment line)	51.40%	Beta	2.63	2.49	[27, 33–36]
Mean time lost (h) for esketamine administration (every treatment line including esketamine)	3	Gamma	25	8.33	[23]
Health state utilities					
Remission	0.918	Beta	168.93	9400.13	TRANSFORM-2 [14]

Table 1 (continued)

Parameter	Base-case value	Distribution	Alpha	Lambda or beta	References
Response	0.899	Beta	141.18	8024.90	TRANSFORM-2 [14]
No-response	0.760	Beta	28.21	1902.07	TRANSFORM-2 [14]

value, equal to 31,283.25€ in 2021 value) [37] for Italian individuals aged 45–54 years (the same age of individuals entering the model). In order to perform long-term projections we considered an average annual salary of 33,367€ [37] (2019 value, equal to 33,600.57€ 2021 value) for individuals aged 55–67 years, with 67 years being the mean retirement age in Italy [38]; we therefore applied the calculated productivity loss of 51.40% in case of non-response to treatment (set to 0 for retired). Similarly, we applied the productivity loss corresponding to 3 h in case of esketamine administration in working-age individuals, considering a working week comprising 40 h [39].

Healthcare resource utilization and costs used in the model are summarized in Table 1 together with the other model parameters.

2.4 Quality-of-Life Estimates

For the estimation of the utility coefficients for the health states of the model, the Italian algorithm has been applied [40] to EuroQol 5D-5L data collected during the TRANSFORM-2 study [14]. Values obtained with the EuroQol questionnaire were 0.899 (SD 0.075) for responders, 0.918 (SD 0.070) for remitters and 0.760 (SD 0.142) for non-responders (Table 1). In the model, the value 0.760 for non-responders has also been applied to relapse and treatment initiation health states.

2.5 Cost-Utility Analysis

The incremental cost-utility ratio (ICUR) was calculated as the difference in the mean expected costs divided by the difference in the mean expected QALYs of the considered strategies. Moreover, the INMB has been calculated as (incremental benefit × WTP) − incremental cost, considering both societal and NHS perspectives.

The model has been run three times, according to the different lines of treatment.

The paucity of theoretical and empirical basis regarding the appropriate way of estimating the WTP threshold did not facilitate the adoption of specific threshold values across the different countries. Around the world, threshold values range from 15,000€ to 80,000€ [41, 42]. In Italy, thresholds vary between 25,000€ and 74,700€ [43–45]. In the context of the present analysis, a WTP of 50,000€/QALY has been applied in the base-case scenario and different analyses have been performed by considering WTP variations in the range 0–100,000€.

The INMB measures the difference in NMB between esketamine plus ADs and ADs alone; a positive INMB would indicate that esketamine plus ADs is a cost-effective strategy compared with ADs at the given WTP threshold. In this case, the cost to obtain the benefit would be less than the maximum amount that the decision maker would be willing to pay for this benefit.

2.6 Sensitivity and Scenario Analyses

Univariate analyses were performed according to the model parameters by applying a variation of ± 20% of baseline values. Moreover, the time horizon has been varied from 0 to 40 years (considering the age of 51 years of patients entering the model, this may represent a lifetime horizon), while for the discount rate, variations between 0 and 10% have been considered.

In addition, a probabilistic sensitivity analysis (PSA) has been performed to test the robustness of the model results. Model parameters were entered into the model along with a distribution, beta for utilities and gamma for costs and relative risks (see Table 1). Where the studies referencing the parameters reported 95% confidence intervals, these were applied to estimate parameters variations, otherwise a standard deviation of 20% of the baseline values has been used. Second-order Monte-Carlo simulations (10,000 iterations) were conducted and the results have been presented as 95% credible intervals around cost difference, QALYs difference and INMB values.

In order to evaluate variations in the model results according to different assumptions, two scenarios were considered in the analyses in addition to the base case (scenario A). In the first one (scenario B), clinical response and clinical remission for esketamine (relative risks versus placebo + ADs) were derived from a meta-analysis including TRANSFORM-1 [13], TRANSFORM-2 [14] and also TRANSFORM-3 [15] trial data, which considered a flexible esketamine dose (28 mg or 56 mg or 84 mg) and patients 65 years of age or older (see Appendix 2 in the ESM for

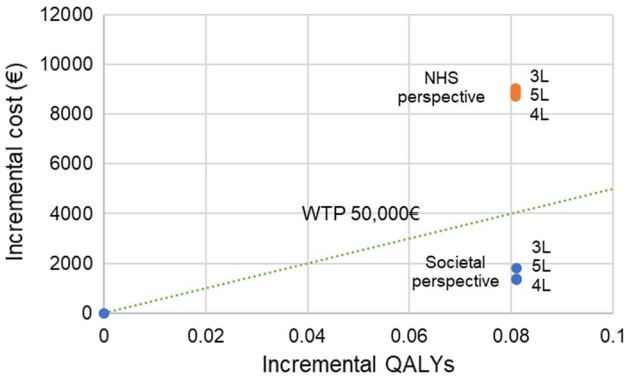


Fig. 3 Summary of cost-effectiveness analysis results of esketamine + antidepressants (ADs) vs ADs alone for the different treatment lines and perspectives

details). Another scenario (scenario C) considered a continuous treatment with esketamine in patients with disease remission instead of a maximum treatment duration of 9 months, thus increasing the long-term free-from-relapse rates from 38% to about 58% [16].

Moreover, best- and worst-case univariate sensitivity analyses have been performed to identify the main cost drivers [41].

3 Results

In the base-case scenario (A), from the societal perspective the model estimated a mean cost per patient undergoing esketamine plus ADs in the range 128,613–133,671€ and a cost for ADs alone of 126,819–132,278€, considering the initiation of esketamine in the different treatment lines, from 3 to 5 (3L–5L); these figures were 85,640–89,379€ and 76,615–80,512€, respectively, considering the NHS perspective. Regarding health outcomes, over the time horizon of 5 years, the model estimated average QALYs in the range 3.781–3.785 and 3.700–3.704, according to the different treatment lines, for patients administered esketamine plus ADs and for those not treated with esketamine, respectively.

Results summarized in the cost-effectiveness plane are reported in Fig. 3, while Fig. 4 shows the acceptability curves and scatterplots with incremental QALYs and costs for the PSA from the societal perspective (see Supplementary Fig. 2 in the ESM for details on the NHS perspective).

The model results based on costs, QALYs, incremental QALYs and costs, ICUR and INMB from NHS and societal perspectives are summarized in Table 2 for the baseline scenario (A) and for the scenarios that consider meta-analyses including the TRANSFORM-3 study (scenario B) or continuous treatment with esketamine in patients in remission (scenario C). The table also shows outcome variations according to the PSA (95% credible intervals). Figure 5 reports the detail of INMB over time for the scenarios considered from the societal perspective (see Supplementary Fig. 3 in the ESM for details on the NHS perspective).

ICURs ranged from 13,493€ to 45,849€ across the different scenarios and treatment lines in the societal perspective, while they were over the threshold of 100,000€ for the NHS perspective scenarios. Considering the WTP of 50,000€/QALY, the probability that esketamine treatment is cost effective compared with ADs in the societal perspective varies in the range 62–65% for the different treatment lines. Considering the INMB, in the base case (5-year horizon), it was always negative from the NHS perspective, while it was positive with a range of 2259€–2744€ across treatment lines from the societal perspective, meaning that in the short term, benefits are greater than costs; similar figures were 2553€–3037€ for scenario B, while Scenario C showed lower INMBs (range 443€–1056€). For the base case, the INMB begins to occur earlier with progression to subsequent lines of treatment (3.9 years for 3L, 3.6 years for 4L and 3.5 years for 5L). The PSA showed great variation around the model results.

One-way sensitivity analyses on the societal perspective revealed that the lifetime horizon leads to the greater INMB (range 18,048€–20,971€ for the different treatment lines). Other parameters impacting on the model results are related to the administration of esketamine (device cost, number of administrations), to utility weights for treatment response and no response and to working time lost. Regarding the NHS perspective, the cost of the esketamine device, the utility weights for response and no response and the time horizon are the most impacting parameters. Figure 6 reports the tornado diagrams for the base-case model for the treatment lines and societal perspective (see Supplementary Fig. 4 in the ESM for details on the NHS perspective).

Best- and worst-case univariate sensitivity analyses identified productivity losses, costs for the management of patients in territorial structures and treatment with esketamine as the main cost drivers.

WTP variations in the range 0–100,000€ showed an increasing trend for the NMB corresponding to the increase in the WTP for all treatment lines with similar trends for 4L and 5L (Fig. 7). This was expected because the model inputs related to clinical outcomes are not different from the fourth line onwards, while costs present only slight variations. Break-even values for the WTP for which the INMB is 0 are about 22,200€, 16,400€ and 17,100€ for 3L, 4L and 5L, respectively. Details on NHS perspective are reported in Supplementary Fig. 5 (see ESM). INMBs for the NHS perspective are negative regardless of the WTP threshold applied.

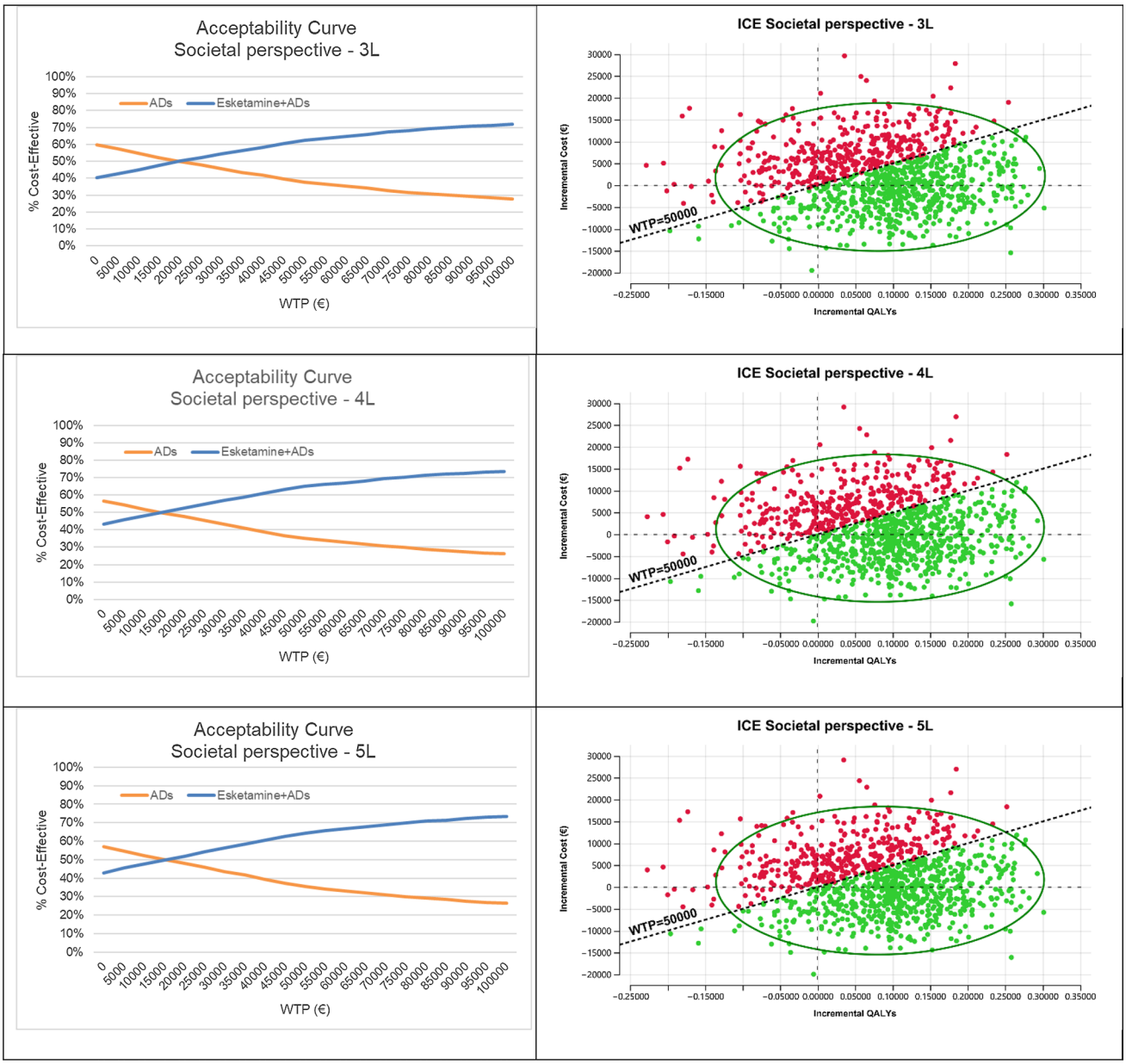


Fig. 4 Acceptability curves and scatterplots for the incremental cost effectiveness (ICE) for the different treatment lines from the societal perspective for the base case

3.1 Model Validation

The 'face validity' of the model has been tested by a psychiatrist who evaluated the inclusion of key features of the disease and of considered treatments. Subsequently, an external validation has been performed using data from sources not used in the model-building process. In particular, the proportions of non-responding patients for ADs projected by the model at 12 months for the different treatment lines have been compared with the same data reported by a recent real-world study published by Heerlein and colleagues [27].

For treatment with ADs alone, the model estimated rates of no response in the range 67–70%, depending on the treatment line considered (from 3 to 5), showing overlapping with the value of 69.2% reported by the real-world study. Afterward, the model results were compared with those presented in the literature in the same context. Two full-text studies were found assessing the cost effectiveness of esketamine versus ADs, both in the US setting [23, 24]. Clinical sources were the same as for our model; both US studies considered esketamine efficacy from the TRANSFORM trials (TRANSFORM-1 and TRANSFORM-2 for [24] and all

Table 2 Model results according to the different perspectives and scenarios considered (esketamine + ADs vs ADs)

Scenarios	Societal perspective			NHS perspective		
	3L	4L	5L	3L	4L	5L
Costs						
ADs (base-case, Scenario A)	126,819€	130,132€	132,278€	76,615€	79,029€	80,512€
ADs (Scenario B)						
ADs (Scenario C)						
Esketamine + ADs (base-case, Scenario A)	128,613€	131,460€	133,671€	85,640€	87,720€	89,379€
Esketamine + ADs (Scenario B)	128,408€	131,254€	133,464€	85,599€	87,678€	89,338€
Esketamine + ADs (Scenario C)	131,714€	134,374€	136,721€	90,542€	92,391€	94,226€
QALYs						
ADs (base-case, Scenario A)	3.70374	3.69986	3.69958	3.70374	3.69986	3.69958
ADs (Scenario B)						
ADs (Scenario C)						
Esketamine + ADs (base-case, Scenario A)	3.78482	3.78130	3.78107	3.78482	3.78130	3.78107
Esketamine + ADs (Scenario B)	3.78659	3.78306	3.78283	3.78659	3.78306	3.78283
Esketamine + ADs (Scenario C)	3.81050	3.80583	3.80561	3.81050	3.80583	3.80561
Delta costs (95% credible interval)						
Base case (scenario A)	1794€ (−10,635; 16,490)	1329€ (−11,136; 15,893)	1393€ (−11,210; 15,914)	9025€ (117; 21,289)	8691€ (−3404; 20,714)	8867€ (52; 20,846)
Scenario B	1589€ (−11,077; 16,454)	1123€ (−11,566; 15,895)	1186€ (−11,566; 15,953)	8984€ (−15; 21,335)	8649€ (−219; 20,772)	8826€ (−37; 20,904)
Scenario C	4895€ (−12,449€; 26,200)	4242€ (−12,863; 25,031)	4444€ (−12,636; 25,493)	13,927€ (1030; 32,749)	13,362€ (803; 31,762)	13,714€ (1201; 32,075)
Delta QALYs (95% credible interval)						
Base-case (scenario A)	0.08107 (−0.10310; 0.24583)	0.08144 (−0.10237; 0.24570)	0.08149 (−0.10221; 0.24576)	0.08107 (−0.10310; 0.24583)	0.08144 (−0.10237; 0.24570)	0.08149 (−0.10221; 0.24576)
Scenario B	0.08285 (−0.10502; 0.25034)	0.08320 (−0.10413; 0.25031)	0.08325 (−0.10408; 0.25030)	0.08285 (−0.10502; 0.25034)	0.08320 (−0.10413; 0.25031)	0.08325 (−0.10408; 0.25030)
Scenario C	0.10676 (−0.12574; 0.29282)	0.10597 (−0.12457; 0.29130)	0.10603 (−0.12455; 0.29151)	0.10676 (−0.12574; 0.29282)	0.10597 (−0.12457; 0.29130)	0.10603 (−0.12455; 0.29151)
ICUR						
Base-case (scenario A)	22,133€ (−580,217; 545,758)	16,314€ (−631,133; 550,374)	17,095€ (−629,842; 551,145)	111,312€ (−1,040,312; 851,566)	106,705€ (−1,002,616; 868,551)	108,806€ (−1,035,517; 874,304)
Scenario B	19,181€ (−559,188; 565,343)	13,493€ (−630,436; 554,173)	14,248€ (−643,098; 578,696)	108,444€ (−1,009,580; 856,392)	103,949€ (−992,448; 792,189)	106,017€ (−1,025,980; 801,623)
Scenario C	45,849€ (−666,748; 811,525)	40,036€ (−613,343; 762,825)	41,909€ (−630,656; 793,822	130,452€ (−1,153,261; 1,209,453)	126,095€ (−971,378; 1,237,826)	129,337€ (−988,986; 1,253,644)

Table 2 (continued)

Scenarios	Societal perspective			NHS perspective		
	3L	4L	5L	3L	4L	5L
INMB (95% credible interval)						
Base-case (scenario A)	2259€ (−15,350; 17,180)	2744€ (−14,843; 17,663)	2681€ (−14,851; 17,643)	−4971€ (−21,496; 7296)	−4618€ (−21,205; 7562)	−4792€ (−21,340; 7356)
Scenario B	2553€ (−15,331; 17,633)	3037€ (−14,732; 18,140)	2976€ (−14,877; 18,164)	−4842€ (−21,569; 7583)	−4489€ (−21,277; 7865)	−4663€ (−21,412; 7625)
Scenario C	443€ (−23,984; 20,568)	1056€ (−23,060; 20,975)	858€ (−23,264; 20,860)	−8589€ (−29,772; 7876)	−8063€ (−29,220; 8065)	−8412 (−29,059; 7634)

ADs antidepressants, *ICUR* incremental cost-utility ratio, *INMB* incremental net monetary benefit, *NHS* National Health Service, *QALYs* quality-adjusted life years

three TRANSFORM trials for [23]) and the clinical efficacy of standard of care (ADs alone) from the STAR*D study; long-term clinical inputs related to continued response to esketamine were derived from the SUSTAIN-1 study. Concerning QALYs, Ross and Soeteman [23], who considered a time horizon of 5 years, report a difference of 0.07 between esketamine and ADs, similar to our result (0.081). The second study [24] considered a lifetime horizon and reported a QALYs difference of 0.19 (0.39 in our case). In the US studies, the cost of esketamine for the first month was higher compared with the cost for Italy (3734.95€) and was in the range US$5572 [23] to US$6826 [24] (about 4690–5746€ in mid-2021), while productivity losses were clearly described in one study [23] and were lower (e.g., 8.4 h/week = 21% of working time lost in non-response health state derived from a single study, compared with our data of 51.40% derived from a meta-analysis considering five studies), probably contributing to highlight the non-cost effectiveness of esketamine compared with ADs alone. If we adapted our model including the main inputs (esketamine efficacy relative to usual care, utility values, direct health care costs per treatment line, lost productivity in the non-response health state, cost of esketamine) from the model by Ross and Soeteman [23], which is the model most similar to ours in terms of structure and time horizon, we would obtain an ICUR of about US$214,000/QALY from the societal perspective, confirming the non-cost effectiveness of esketamine in this context.

4 Discussion

Treatment-resistant depression occurs commonly in up to 30% of treated MDD patients and represents a great economic burden, showing high outpatient medical costs, more frequent hospitalizations and high indirect costs [46]. Different studies have shown that 21–29% of costs are direct health costs while indirect or associated costs due to lost occupational productivity (indirect non-health costs) may account for up to 79% of the total costs of depression [47]. With TRD being a chronic condition with repercussions for the NHS but especially on working and relational spheres, the present study aimed to perform a cost-utility analysis from the societal perspective in order to support decision makers in assessing the value of intranasal esketamine for patients with TRD in Italian clinical practice. Intranasal delivery showed advantages compared with oral and intravenous administration routes [48], including lower doses administered and consequently reduction of adverse events. Other possible advantages are the non-invasive administration, shorter time to onset of effect and higher bioavailability due to avoidance of hepatic first-pass metabolism. Moreover, self-administration may be an option to be evaluated in order to allow wider general use.

Considering a time horizon of 5 years, treatment with esketamine + ADs compared with ADs alone from the societal perspective in Italy showed to be a cost-effective strategy with ICUR in the range 22,934–28,877€, with a positive INMB in the range 1712€–2204€, with probabilities of being cost effective in the range 62–64%, according to the different treatment lines (3L–5L). From the NHS perspective, esketamine in combination with ADs led to a negative INMB. These results emphasize that a narrow perspective of the analysis, limited to the NHS, may underestimate the potential benefits of a treatment that would increase patients' productivity and well-being.

Sensitivity analyses showed that, for all the treatment lines, the parameters most impacting the INMB were the cost of treatment with esketamine, health states utilities for response and no response and the weekly productivity losses per patient. The lifetime horizon for the analyses reported the greater advantages in terms of INMB for the

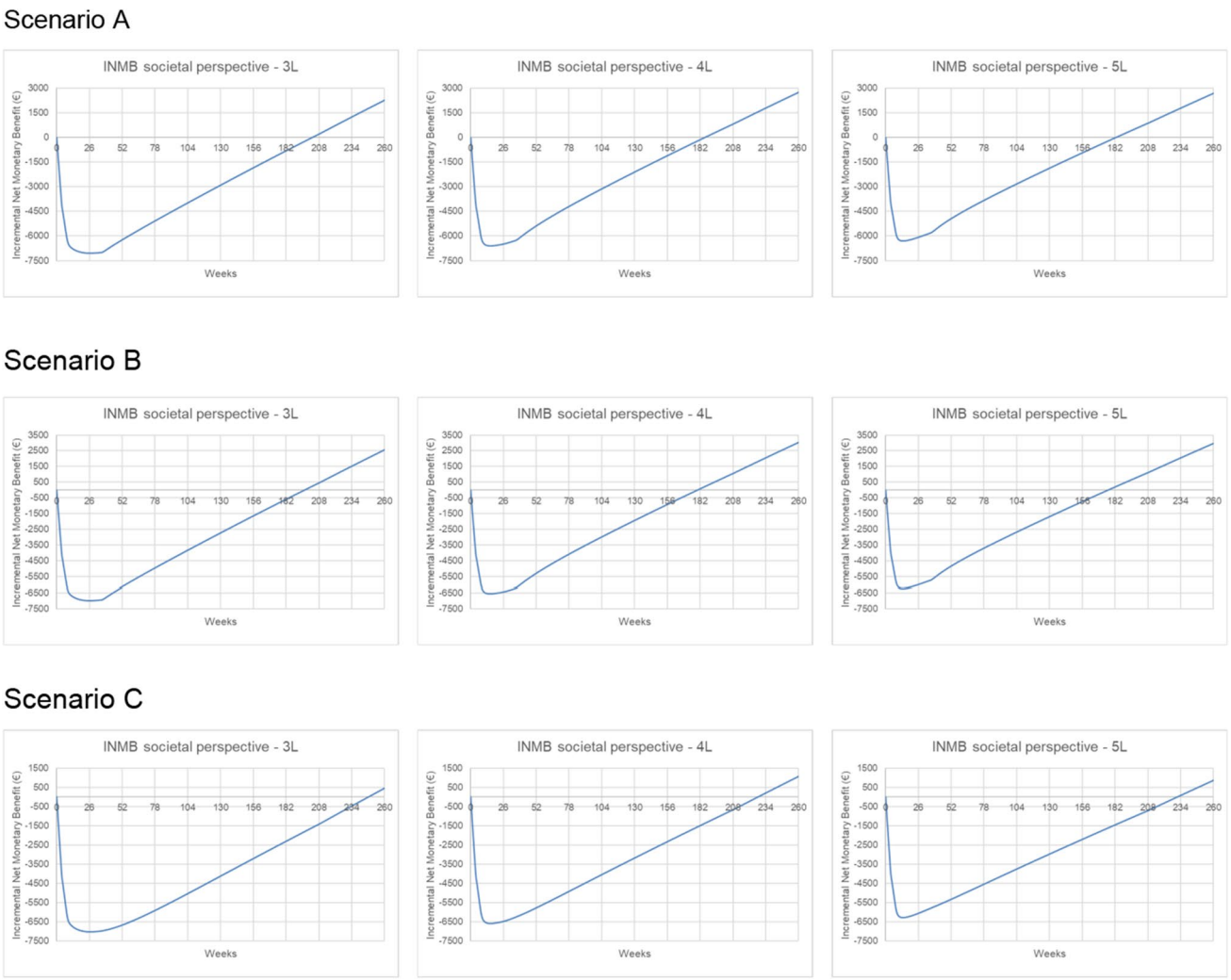


Fig. 5 Incremental net monetary benefit (INMB) over time for the societal perspective for the different treatment lines and scenarios considered

societal perspective. The model considers different scenarios in which esketamine treatment is started in third, fourth or fifth line; the similarity of the INMB curves shows that the efficacy of esketamine is maintained across the different treatment lines. The lowest point of the single curve is related to the high investment cost for esketamine that does not give immediate benefits, but rather benefits over time. The analyses showed also that the advantage in terms of INMB is maintained for a wide range of societal preferences expressed by WTP thresholds, and in particular for values above 28,800€, 23,000€ and 23,600€ for 3L, 4L and 5L, respectively. When adopting the societal perspective, a 'demand-side threshold' should be chosen in order to reflect the societal preferences [49]; however, there may be difficulties in assessing the preferences in terms of WTP of patients with TRD because of their psychosocial impairment [50] and for the purpose of the base-case analysis we relied on the arbitrary threshold of 50,000€/QALY.

In literature, the evaluation of esketamine combined with ADs is performed through cost-effectiveness analyses, which report conflicting results. The study by Ross and Soeteman [23], which considers both societal and NHS perspectives and a time horizon of 5 years, showed that esketamine + ADs is not a cost-effective option considering the current price in the US. A report published by the Institute for Clinical and Economic Review [24] estimated incremental cost-effectiveness ratios of esketamine + ADs vs ADs alone of approximately US$198,000 per QALY gained and approximately US$2.6 million per life-year gained, considering a lifetime horizon. In both cases, the results were above the commonly cited cost-effectiveness thresholds. Another abstract [51], still considering the US context, showed that the resulting incremental cost per QALY gain, from a societal and payer's perspective over a time horizon of 5 years, was below a WTP threshold of US$100,000 per QALY gained, highlighting that esketamine was a cost-effective

treatment alternative to ADs for patients with TRD. The first two studies [23, 24] considered esketamine efficacy from TRANSFORM trials, clinical efficacy of ADs alone from the STAR*D study and long-term clinical inputs related to continued response of esketamine from the SUSTAIN-1 study. The cost of esketamine for the first month was in the range US$5572 [23] to US$6826 [24]. On the other side, the abstract by Hernandez and colleagues [51] reports only that transition probabilities, relapse rates, and utility scores were retrieved from esketamine trials without reporting details on the esketamine cost or other input data to allow comparisons. In the model validation process, we highlighted that US models used higher costs for treatment with esketamine and lower productivity losses compared with the Italian data, thus leading to the non-cost-effective profile of the innovative treatment.

The present study has a number of limitations that need to be recognized. First, the model results are mainly influenced by efficacy data of esketamine derived from published RCTs, one of which (TRANSFORM-1, considering esketamine 84 mg + ADs [13]) reported a higher rate of clinical remission compared with ADs alone but with a borderline statistical significance, which was reflected in the meta-analysis results. The lack of robust statistical significance for esketamine 84 mg + ADs may be due to the drop-out rate that was 3-fold higher compared with the comparator. Although no clear trend in the reasons for discontinuation was identified, the generalizability of the outcomes to a broader real-world setting should be performed with caution. Concerning the drop-out rates, in TRANSFORM-1 and TRANSFORM-2 trials, 3.5% and 7% of patients, respectively, discontinued esketamine due to adverse events and the meta-analyses on remission and response rates were influenced by such treatment discontinuations. The recent real-world study by Samalin and colleagues [52], performed on a limited number of patients ($N = 66$), reported a slightly higher drop-out rate for adverse events of 9%, thus probably lowering the real efficacy of the nasal treatment.

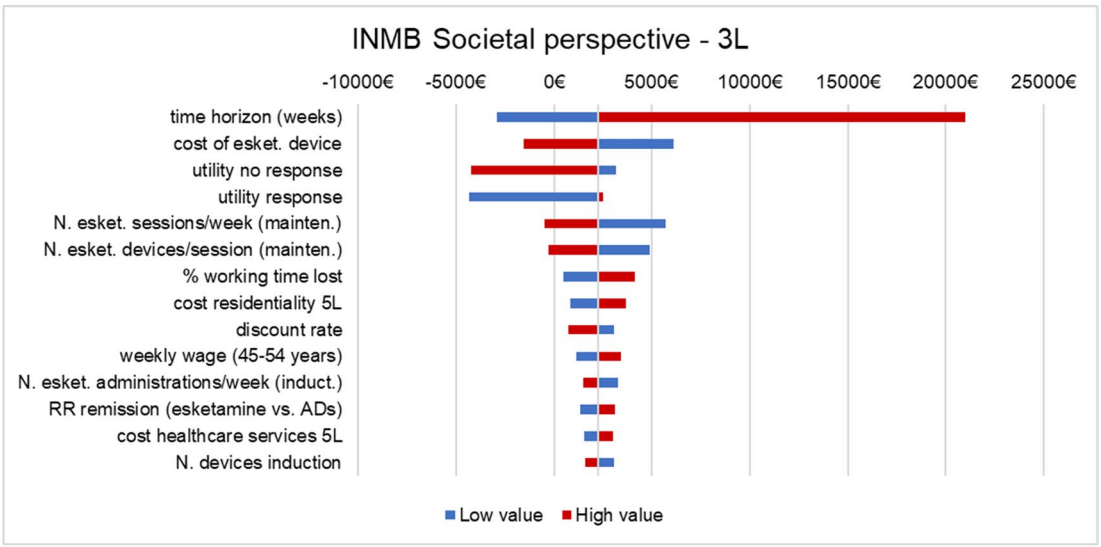
Efficacy data of antidepressants for TRD patients were retrieved from a single study (STAR*D) [6]; however, the study is representative of a population of patients with non-psychotic MDD, treated according to the standard of care in up to four different treatment steps. Patients not achieving adequate clinical response after the second treatment step are considered to be affected by TRD according to definitions presented in the recent literature [9]. Even though the STAR*D sample comes from US, considering the characteristics and the treatment approach of this cohort, the results are generalizable to the European and Italian settings.

The model considers a maximum number of treatment lines equal to six and it is assumed that relapsing patients are eligible for subsequent treatments till the sixth line; after that, if the patient does not respond, he/she will not undergo further therapies. This assumption may have overestimated the clinical benefit of the treatments, however the overestimation should have been the same for both treatment strategies (ADs alone and esketamine + ADs), limiting the possible influence on the comparative model results. Another point is regarding the treatment effects that were assumed the same from the fifth line onwards. In this case the assumption may have overestimated the clinical benefits of the treatments as it is likely that the rates of remission and response decrease when the treatment lines increase. Again, the overestimation should be referred to both treatment strategies, thus limiting the influence on the model outcomes.

Other limitations relate to costs; from the societal perspective, the model considered only productivity losses that were applied to the non-response health states of the different treatment lines. Although the greater cost component for the societal perspective is loss of working productivity [35], the inclusion of out-of-pocket costs would have provided an improvement of the cost-utility profile of the use of esketamine for the treatment of TRD. Moreover, the reference study that we used to retrieve costs for TRD patients in Italy [32] reported an analysis of administrative data collected from 2011 to 2017. Unfortunately, the paper neither specified if the costs were uplifted to 2021, which was the year of publication, nor reported details on the reference years for the single data collected (it reported only mean costs), thus not allowing us to make any costs uplifts. On the other side, an increase in these costs due to uplifting would have improved the cost-effectiveness profile of esketamine compared with ADs.

Finally, we considered a limited time horizon (5 years) for our base-case analyses. Although TRD can be considered a chronic condition following the failure of other therapies, a lifetime horizon would have required substantial extrapolations of data in order to populate the model, so only an exploratory sensitivity analysis in this context has been performed. We therefore followed the approach already reported by Ross and Soeteman [23] and considered a time horizon of 5 years for the base case since this can be considered a significant period for the perspective of patients' care.

Despite these limitations, the present study provides an estimate of the cost-utility profile of esketamine combined with ADs compared with ADs alone for the treatment of TRD in Italy. In contrast to the studies already published in the literature [23, 24], the present study considers the management of patients with TRD across the different treatment lines, considering initiation of esketamine in combination with other antidepressants from the third to the fifth. Although the results reflect the Italian perspective, the presentation of healthcare resources consumption in natural units, as suggested by EUnetHTA guidelines [53], may be useful when performing cost adjustments for other regions or countries.


INMB Societal perspective - 3L
-10000€
-5000€
0€
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15000€
20000€
25000€
time horizon (weeks)
cost of esket. device
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N. esket. devices/session (mainten.)
% working time lost
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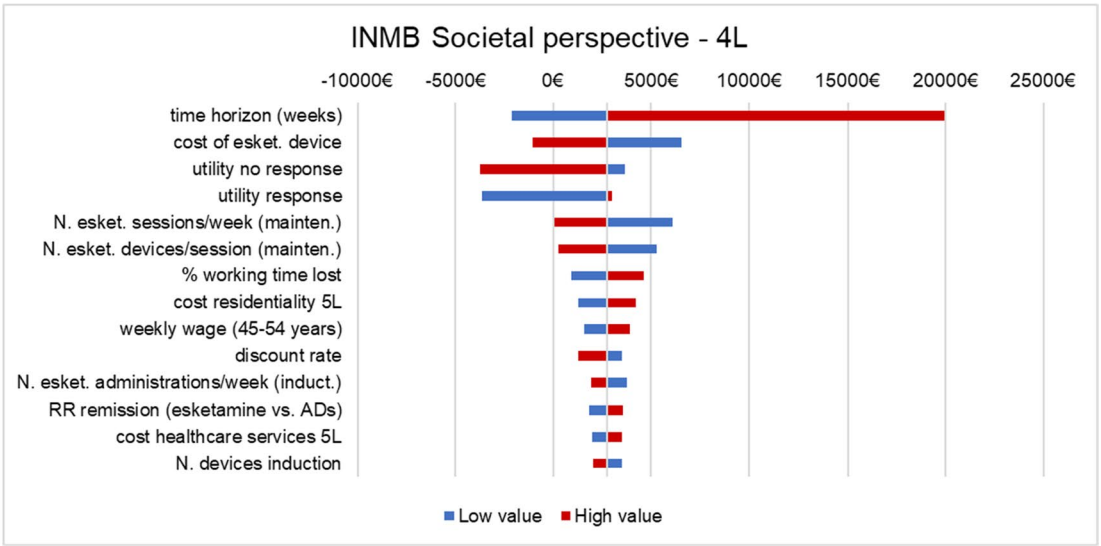
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time horizon (weeks)
cost of esket. device
utility no response
utility response
N. esket. sessions/week (mainten.)
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% working time lost
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weekly wage (45-54 years)
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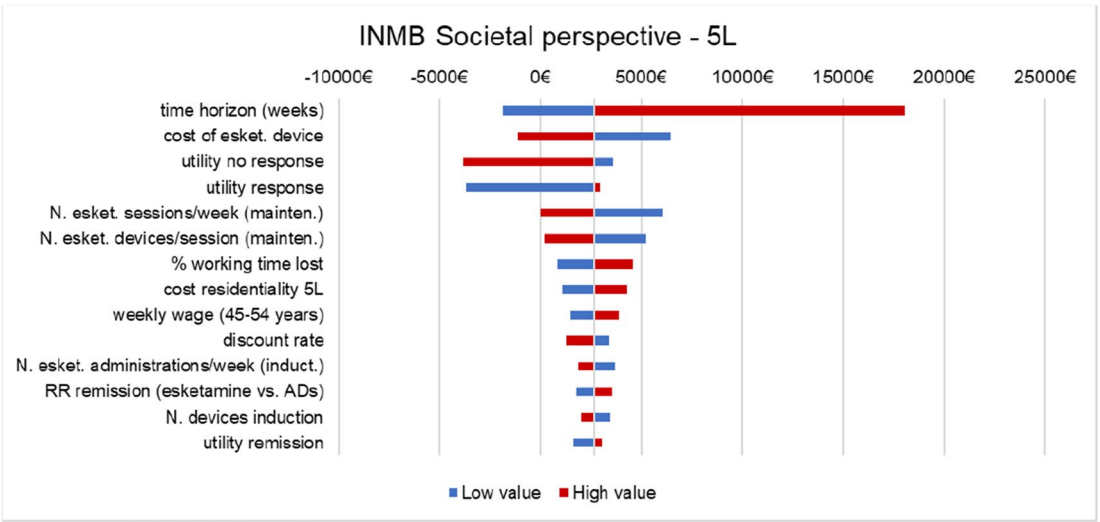
RR remission (esketamine vs. ADs)
cost healthcare services 5L
N. devices induction
Low value
High value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discount rate
N. esket. administrations/week (induct.)
RR remission (esketamine vs. ADs)
N. devices induction
utility remission
Low value
High value

◂**Fig. 6** Tornado diagrams reporting one-way sensitivity analyses on INMB for the base-case in the societal perspective. *ADs* antidepressants, *INMB* incremental net monetary benefit, *RR* relative risk

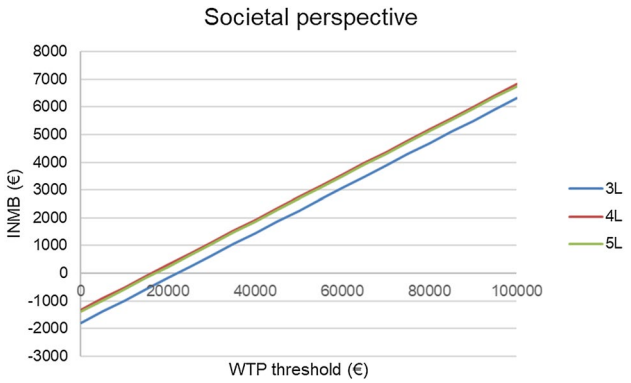

Fig. 7 INMB variations according to different WTP values for the societal perspective. *INMB* incremental net monetary benefit, *WTP* willingness to pay

5 Conclusions

The present study provides a comprehensive evaluation of the clinical pathways of patients with treatment-resistant depression treated with antidepressants alone or combined with esketamine. The analyses showed that esketamine may be a cost-effective opportunity from the societal perspective for the management of patients with TRD. The incremental net monetary benefit of esketamine treatment compared with antidepressants is positive and begins to occur earlier with progression through subsequent lines of treatment, from third to fifth. The study highlights that a more costly treatment for the NHS may be viewed as an investment able to provide greater future benefits for the society as a whole, allowing continuous improvement of the treatment process according to the value-based healthcare paradigm [54].

In the future, data collected from observational studies or registries, which can also include the collection of productivity losses and costs sustained by the patients, will be able to provide further evidence in order to improve the reliability of the model results.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40273-022-01220-z.

Declarations

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Conflict of interest The authors do not declare any conflict of interest.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Data availability The data used to populate the model for the analyses presented in our manuscript are data published in the literature. We did not develop specific software code to perform the analyses.

Code availability Not applicable.

Author contributions Conceptualization: PA, FC; Methodology: CR, PA, FC; Formal analysis and investigation: CR; Writing - original draft preparation: CR; Writing - review and editing: CF, PA, FC; Funding acquisition: PA, FC; Resources: CR, PA, FC, CF; Supervision: PA, FC.

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