



Switching “Real-World” Diabetes Patients to Degludec from Other Basal Insulins Provides Different Clinical Benefits According to Their Baseline Glycemic Control

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ABSTRACT

Introduction: The stable, ultra-long duration of action of insulin degludec (degludec) minimizes fluctuations in glucose-lowering activity over the daily (24-h) dosing period, and comparative studies with other basal insulins suggest that these properties translate into a lower risk of hypoglycemia at equivalent levels of glycemic control. Results from the real-world European multicenter, retrospective chart review study of

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2550 patients with type 1 and type 2 diabetes (T1D and T2D) in routine clinical care EU-TREAT (NCT02662114) showed that patients benefited from improved glycemic control and significantly reduced rates of hypoglycemia following a switch to degludec.

Methods: In this post hoc analysis, EU-TREAT patients were stratified into good ($\leq 7.5\%$ HbA1c), intermediate (> 7.5 to $\leq 8.5\%$ HbA1c), and poor ($> 8.5\%$ HbA1c) glycemic control at baseline to investigate the possibility of differential benefits, either improved control or reduced risk of hypoglycemia, whichever the need. Changes in HbA1c, overall hypoglycemia, and total insulin dose from baseline to 6 and 12 months follow-up were assessed for each group.

Results: For both T1D and T2D patients, those in good initial control experienced significant reductions in rates of hypoglycemia and total insulin dose following the switch, without compromising control. Those in poor initial control achieved significant improvements in HbA1c with no change in rates of hypoglycemia or total insulin dose.

Conclusion: This analysis expands the findings of EU-TREAT by showing differential changes in the clinical endpoints depending on particular need. It introduces the possibility that the differential benefits of degludec could address two of the renowned clinical challenges faced when treating diabetes: improving glycemic control for optimal management of T1D and titrating

insulin dose in T2D, both without fear of increased hypoglycemia.

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Keywords: EU-TREAT study; Glycemic control; Hypoglycemia; Insulin degludec; Long-acting insulin; Observational study; Post hoc analysis; Type 1 diabetes; Type 2 diabetes

INTRODUCTION

Insulin degludec (degludec) is a basal insulin with a unique mode of protraction, conferring an ultra-long duration of action (exceeding 42 h at relevant clinical doses in patients with type 1 diabetes, T1D) and a stable glucose-lowering profile over the 24-h dosing period [1–3]. Effective insulin therapy commonly requires dose intensification, yet this process is often restricted by experience and/or fear of hypoglycemic events [4, 5], their accompanying negative physical, societal, and psychological consequences, and loss of productivity [4–8]. In a multinational, cross-sectional survey of physician and patient attitudes to insulin, the majority (88%) of responding physicians admitted many patients fell short of target HbA1c levels, yet dose increases were hindered because of fear of hypoglycemia [5, 7]. This exemplifies the “barrier of hypoglycemia” [4] which can compromise treatment [9].

The European multicenter, retrospective, non-interventional chart review study EU-TREAT (NCT02662114) was a real-world study of 2550 patients with diabetes (1717 with T1D and 833 with type 2 diabetes, T2D) in routine clinical care across six countries in Europe. EU-TREAT investigated the changes in clinical characteristics (HbA1c, hypoglycemia, and total insulin dose) that followed a switch to degludec from another basal insulin [10]. As EU-TREAT was a large-scale study of the use of degludec in routine clinical practice, the data encompass the impact of factors such as clinical setting, provider, lifestyle, environment, and health system on the outcomes of treatment with degludec. Thus, the data can address different

questions to the standard efficacy and safety investigations of randomized clinical trials [11, 12]. Mean results showed that in both T1D and T2D, switching was associated with improved glycemic control, reduced rates of hypoglycemia, and reduced total insulin doses [10]. As around one-third of patients were already in good control at baseline (36.9% T1D and 28.5% T2D had HbA1c < 7.5%), the switch to degludec was not driven solely by a desire to improve HbA1c [10]. Switching was motivated by blood glucose variability in approximately 70% of patients and it is possible that the pre-switch insulin prompted a heterogeneous response, whereby some patients achieved good glycemic control at the cost of suffering hypoglycemic events, while others achieved tolerability at the cost of suboptimal control [10]. Most modern studies of insulin treatments have a treat-to-target design, investigating differences in hypoglycemic events at HbA1c parity. Predominantly compared with insulin glargine U100, degludec has consistently been shown to reduce hypoglycemic risk in such studies [10, 13–16]. It seems logical that patients with control restricted by the “barrier of hypoglycemia” [4] could safely switch to degludec and improve control, whereas those in good control yet experiencing hypoglycemia could switch to improve tolerability whilst maintaining control.

In this post hoc analysis we have used data from EU-TREAT to test if the complementary benefits (improved glycemic control or reduced rates of hypoglycemia, dependent on individual need) are achieved in a real-world setting. As baseline HbA1c has been identified as the strongest predictor of achieving glycemic control, we performed the analysis on data from EU-TREAT patients stratified into three groups of different levels of baseline HbA1c [17].

METHODS

The detailed study design and methodology of the EU-TREAT study have been described previously [10]. To summarize, data were collected from the medical records of patients with T1D or T2D across Europe who had been treated

with degludec after switching from another basal insulin [10].

Patients were required to have switched to degludec [\pm oral antidiabetic drugs (OADs) \pm prandial insulin] from any other basal insulin (\pm OADs \pm prandial insulin) at least 6 months before data collection [10]. Here, we stratified patients into the following categories of glycemic control at baseline, chosen to represent an equal number of patients and reflect common real-world clinical scenarios, where patients are not necessarily treated to HbA1c < 7%:

- Good control (HbA1c \leq 7.5%)
- Intermediate control (HbA1c > 7.5 to \leq 8.5%)
- Poor control (HbA1c > 8.5%)

Endpoints were change in HbA1c, overall hypoglycemia, and total insulin dose from baseline to 6 and 12 months' follow-up. A hypoglycemic event was defined as any episode of hypoglycemia recorded by the healthcare providers in patient charts [10]. The EU-TREAT study was conducted in accordance with the Declaration of Helsinki (2013 amendment) and written informed consent from all patients was obtained before enrolment. The study protocols were approved according to local regulations by appropriate health authorities and by institutional review boards (see Supplementary Table S1) at all participating institutions. The analysis reported here does not contain any studies with human participants or animals performed by any of the authors.

Statistical Analysis

Analyses of baseline characteristics, demographics, and primary data have been described previously [10]. Data were recorded to reflect two periods of medical history: before (pre-switch) and after (post-switch) the date of degludec initiation. Baseline was defined as the most recent recording during the 3-month period prior to switch.

Pre- and post-switch outcome data were collected at 6 ± 3 and 12 ± 3 months prior to and following switch, as per methodology described previously [10]. Six-month data were

available for all patients with T1D and T2D; 12-month data were available for 76% of those with T1D and 72% of those with T2D [10]. Changes in HbA1c and mean daily insulin doses at the + 6-month and + 12-month time points were analyzed using analysis of covariance (ANCOVA), and the - 12-month and - 6-month data were used to validate results. The changes were modeled as a function of the baseline value and relevant covariates that included country, age, body mass index (BMI), gender, diabetes duration, duration of insulin therapy, and type of basal injections. Least-squares (LS) mean estimates for the changes were reported, with associated 95% confidence intervals and *p* values as appropriate [10]. The number of hypoglycemic events per patient-month at baseline was estimated from counts of events during the 6 months pre-switch. Numbers of events per patient-month at the + 6-month and + 12-month time points were estimated from counts during these periods [10]. Rate data were analyzed using a negative binomial regression estimator, which included a variable to capture differential exposure across patients and a variable to capture the effects of pre- and post-switch [10].

RESULTS

Baseline and Clinical Characteristics

A total of 2550 patients were included in the study (T1D, *n* = 1717; T2D, *n* = 833). Baseline demographics and clinical characteristics of stratified patient groups are presented in Table 1.

Subgroup Clinical Endpoints

The 6- and 12-month changes in HbA1c, hypoglycemia rates, and insulin doses for the stratified T1D and T2D patient groups are shown in Fig. 1i, ii, respectively. At both time points, T1D and T2D patients in good glycemic control at baseline benefited from reductions in rates of hypoglycemia and total insulin dose while still maintaining glycemic control. For

Table 1 Baseline demographics of patients stratified according to glycemic control

Baseline characteristic	T1D			T2D		
	Glycemic control at baseline (%HbA1c)			Glycemic control at baseline (%HbA1c)		
	Good (≤ 7.5)	Intermediate (> 7.5 to ≤ 8.5)	Poor (> 8.5)	Good (≤ 7.5)	Intermediate (> 7.5 to ≤ 8.5)	Poor (> 8.5)
Full analysis set, <i>n</i>	634	642	441	237	283	313
Age, years	48.2 (15.4)	48.4 (15.6)	46.0 (15.7)	66.9 (10.3)	65.7 (9.5)	61.9 (11.0)
Female/male, %	42.6/57.4	45.6/54.4	50.1/49.9	42.6/57.4	41.0/59.0	43.5/56.5
Weight, kg	76.3 (16.5)	78.1 (15.5)	76.7 (16.1)	95.2 (23.1)	93.8 (18.5)	99.3 (21.1)
BMI, kg/m ²	25.9 (5.0)	26.6 (4.6)	26.4 (4.7)	33.4 (6.7)	32.6 (5.4)	34.6 (6.6)
HbA1c, %	6.9 (0.5)	8.0 (0.3)	9.6 (1.1)	6.9 (0.5)	8.1 (0.3)	9.7 (1.1)
HbA1c, mmol/mol ^a	52	64	81	52	65	83
FPG, mg/dL	152.4 (56.1)	161.4 (59.3)	180.7 (69.8)	158.8 (41.6)	162.0 (41.5)	205.3 (64.7)
History of diabetes						
Duration of diabetes, years	22.4 (14.3)	22.3 (13.4)	20.0 (12.2)	19.4 (8.0)	17.4 (8.8)	16.1 (7.2)
Duration of insulin treatment, years	21.7 (14.4)	21.8 (13.3)	19.6 (12.2)	10.7 (6.6)	9.3 (6.5)	9.3 (5.7)
Insulin therapy before degludec initiation						
Insulin regimen: basal-only/basal-bolus/ unknown, %	0/99/1	0/98/2	0/98/2	21/77/3	21/76/2	25/72/4
Basal insulin: glargine U100/detemir/other, %	50/43/6	55/39/6	49/46/5	24/56/20	41/40/19	28/54/19
						19

Table 1 continued

Baseline characteristic	T1D		T2D		Overall
	Glycemic control at baseline (%HbA1c)		Glycemic control at baseline (%HbA1c)		
	Good (≤ 7.5)	Intermediate (> 7.5 to ≤ 8.5)	Good (≤ 7.5)	Intermediate (> 7.5 to ≤ 8.5)	
Basal insulin dosing: OD/BID/unknown, %	50/46/4	51/45/4	56/30/14	65/26/9	62/28/10
		48/47/5			65/29/6

Values are mean (SD) unless otherwise stated

BID twice daily, BMI body mass index, *detemir* insulin detemir, *FPG* fasting plasma glucose, *glargine U100* insulin glargine 100 units/mL, *HbA1c* glycated hemoglobin, *n* number of patients, *OD* once daily, *SD* standard deviation, *T1D* type 1 diabetes, *T2D* type 2 diabetes

^a Calculated, not measured

those with T1D ($n = 634$; mean HbA1c 6.9%), there was a minor, clinically insignificant mean increase in HbA1c (0.1%), and reductions in rates of hypoglycemia were 16% at 6 months and 23% at 12 months. For those with T2D in good control ($n = 237$), large rate reductions of 67% and 73%, respectively, were achieved ($p < 0.05$). Total insulin dose for T1D and T2D patients in good control was reduced by 5.4 and 6.5 mean units, respectively, at 6 months, with similar results at 12 months ($p < 0.05$).

T1D and T2D patients in intermediate glycaemic control at baseline benefited from both reductions in mean HbA1c ($- 0.2\%$ and $- 0.3\%$, respectively) and in rates of hypoglycemia (27% and 66%, respectively) at 6 months, with similar results at 12 months ($p < 0.05$).

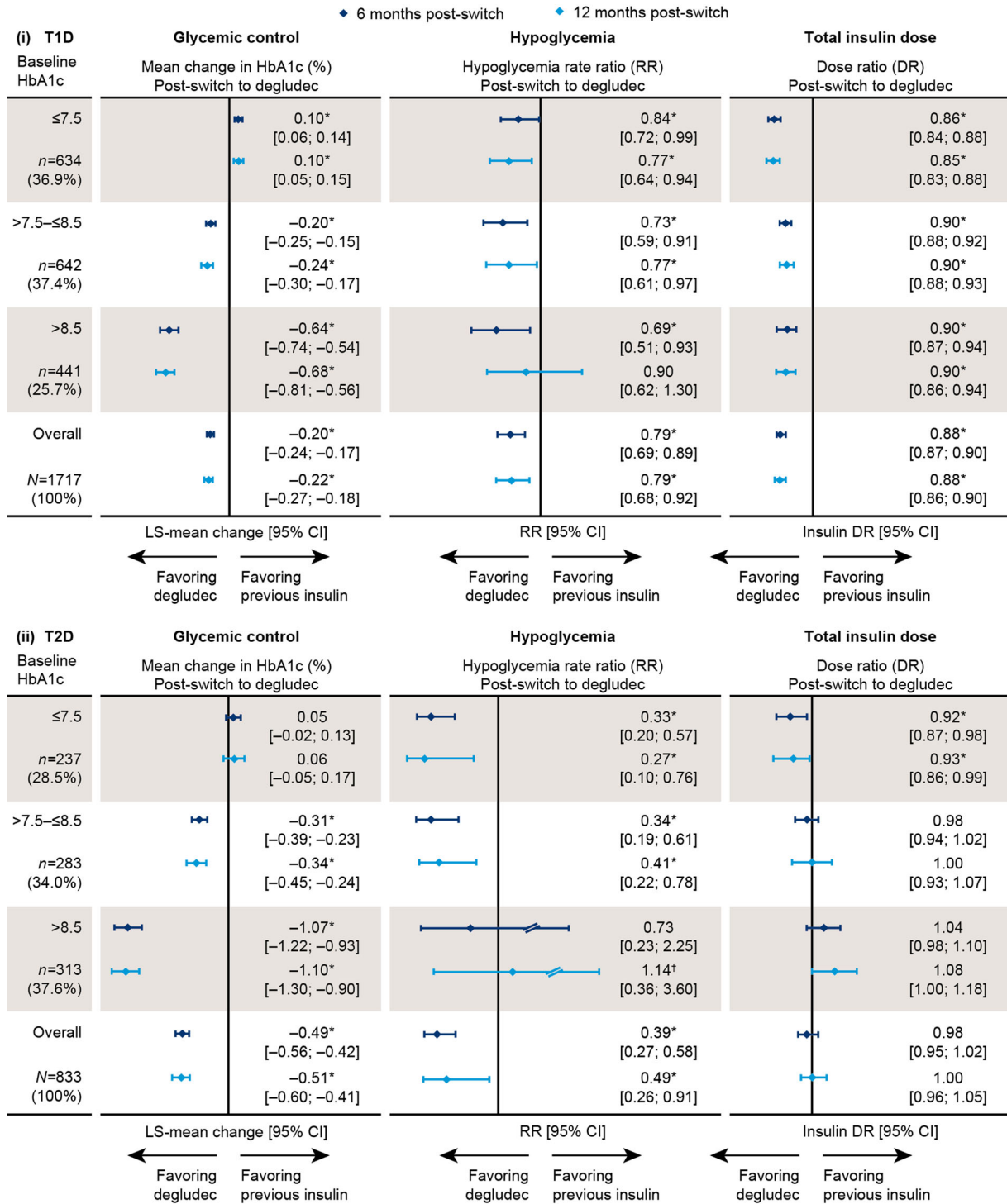
All patients in poor glycaemic control at baseline benefited from clinically significant (in excess of $- 0.64\%$) mean reductions in HbA1c, with reductions in excess of $- 1.05\%$ for patients with T2D, at both 6 and 12 months ($p < 0.05$).

For all stratified patients with T1D, insulin dose and rates of hypoglycemia were significantly reduced by at least 10% at both 6 and 12 months, although the reduction in hypoglycemia at 12 months was relatively small (10%) and not statistically significant for those in poor control ($p = 0.5583$) (Fig. 1i).

Concerning concomitant OADs, there were no changes in mean dosage or number of agents used, and the number of prandial insulin injections for T2D patients recorded at the point of switching to degludec and thereafter remained comparable.

DISCUSSION

This post hoc analysis expands the findings from EU-TREAT by showing how changes in clinical endpoints varied between patients of different glycaemic status at baseline. We have discerned that patients most in need of further glycaemic control achieved improvements greater than the mean, while patients most in need of reduced hypoglycaemic risk also achieved benefits beyond the mean. Each group



◀**Fig. 1** Changes in clinical outcomes at 6 and 12 months post-switch for patients with (i) T1D and (ii) T2D in the EU-TREAT trial stratified according to baseline glycaemic control. ≤ 7.5 = good glycaemic control; $> 7.5 - \leq 8.5$ = intermediate glycaemic control; > 8.5 = poor glycaemic control. * $p < 0.05$, †estimated using Poisson regression due to convergence issues. All changes are from baseline. n = number of patients within each HbA1c group, N = total number of T1D/T2D patients. Analysis of glycaemic control: data are LS-mean change. Multivariate ANCOVA model controlled for country (when appropriate), age, BMI, gender, diabetes duration, duration of insulin therapy, and type of basal injections. Analysis of hypoglycemia: negative binomial regression model controlled for age, BMI, gender, diabetes duration, and duration of insulin therapy. Analysis of total insulin dose: data are log-transformed dose ratios (6- or 12-month total insulin dose/baseline total insulin dose) based on units per kilogram of body weight. Multivariate ANCOVA model controlled for country (when appropriate), age, BMI, gender, diabetes duration, duration of insulin therapy, and type of basal injections. ANCOVA analysis of covariance, BMI body mass index, CI confidence interval, DR dose ratio, LS least-squares, RR rate ratio, T1D type 1 diabetes, T2D type 2 diabetes

better fulfilled their respective clinical needs, without compromising the other endpoint.

Hypoglycemia is a problematic treatment complication. The global Hypoglycemia Assessment Tool (HAT) observational study of more than 27,000 insulin-treated patients with diabetes revealed incidences more than 10-fold higher than previously reported, of 73.3 (T1D) and 19.3 (T2D) events per patient-year [9].

Hypoglycemia is a life-long risk in T1D, which requires full insulin replacement therapy, and the average patient suffers several asymptomatic and symptomatic episodes each week [4]. These episodes are commonly triggered by bolus insulin, which was taken by all T1D patients accounted for in this study and could have influenced the smaller rate reduction experienced by those in good control, compared with T2D patients (16% vs. 67% at 6 months). The reduction is impressive nonetheless, given T1D patients' increased hypoglycemic vulnerability, and our results are consistent with observations in the SWITCH 1 and SWITCH 2 studies [14, 15].

Currently, the only proven clinical option for improving T1D control without introducing additional hypoglycemic risk is insulin pump

therapy, but results from this post hoc analysis present switching to degludec as a promising alternative. Although a very minor (0.1%) but statistically significant increase in HbA1c was seen among patients with T1D and in good glycaemic control, this is below the level of 0.5% which physicians are reported to consider a clinically relevant change [18]. This group also had the highest percentage reductions in insulin dose and significant reductions in hypoglycemic risk, which could reflect a conservative clinical strategy: physicians may have reduced treatment intensity to contain further risk of hypoglycemia.

In late-stage T2D following initiation of insulin treatment, the risk, frequency, and severity of hypoglycemic episodes tend to increase substantially, to approach the T1D scenario [4]. The barrier of hypoglycemia responsible for delaying insulin initiation and reluctance to intensify dose can result in protracted hyperglycemia and attendant morbidity [4]. The significant reduction in rates of hypoglycemia experienced by T2D patients in good control following a switch to degludec introduces an opportunity to circumvent this barrier with a treatment that achieves glycaemic control without an increase or even a reduction in the risk of hypoglycemia [4, 9]. Patients with T2D in poor initial glycaemic control benefited from the greatest improvements across all stratified groups. This could partly be due to the fear of dose intensification resulting in their prior maintenance on lower-than-optimal doses of pre-switch insulin. It might be anticipated that this fear may diminish following switch to degludec, as patients experience improvements in control without additional hypoglycemic events [5]. Most of these patients were at an advanced stage of disease, with 70% on bolus therapy, and therefore difficult to treat because of increased hypoglycemic risk [4]. As such, they were likely to have had the greatest scope for improvement and therapy intensification. In T2D patients overall, the benefits observed can confidently be ascribed to degludec, as there were no changes in concomitant OAD regimens or in the use of other insulins.

Limitations of this analysis mirror those of the primary study, including its observational,

retrospective design and the lack of a comparator arm, which prevented investigating how the effects observed after switching to degludec would compare to switching to an alternative basal insulin. Collection of data was restricted to those data recorded in patient medical charts, which probably included only a subset of the true number of hypoglycemic events. Such under-recording of hypoglycemic events, however, would likely have been equal across the three stratified groups and therefore not impact the calculated rate ratios. The restricted data, together with limitations in analysis, have made it impossible to capture the periodic fluctuations in blood glucose levels that prompted the switch to degludec for most patients despite their adequate average HbA1c control. Despite these limitations, our data nevertheless represent a valuable addition to findings from the degludec clinical trials [13].

There are two noteworthy advantages: as the primary study was a real-world study conducted outside the closely controlled clinical trial setting, its findings have high external validity. There is growing interest in the potential of real-world evidence to complement findings from randomized clinical trials, as the latter are not generalizable to the diverse group of patients found in normal clinical practice [11, 12]. In addition, this was a large-scale study of a significant number of patients. The few other published observational studies involving a switch to degludec are limited in size, population (T1D or T2D), and duration of follow-up [19–23]. One smaller-scale study, however, has findings that support our results. Of 211 patients with T2D switched from alternative basal insulins to degludec, those in poor control (HbA1c > 8.5%) benefited from a greater reduction in HbA1c compared with the overall population ($1.0 \pm 1.1\%$ vs. $0.58 \pm 1.0\%$, $p < 0.001$) [19].

CONCLUSION

In routine clinical practice, switching from other basal insulins to degludec offers differential clinical benefits for patients with diabetes, according to baseline glycemic control. Patients

who switch while in good control benefit from significant reductions in rates of hypoglycemia and total insulin dose, without compromising control. Patients who switch while in poor glycemic control achieve significant improvements in control, with no increase in rates of hypoglycemia or total insulin dose.

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Compliance with Ethics Guidelines. The EU-TREAT study was conducted in accordance with the Declaration of Helsinki (2013 amendment) and written informed consent from all patients was obtained before enrolment. The study protocols were approved according to local regulations by appropriate health authorities and by institutional review boards (see Supplementary Table S1) at all participating institutions. The analysis reported here does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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