Baseline Characteristics Associated With Clinical Improvement in Hospitalized Patients With Moderate COVID-19

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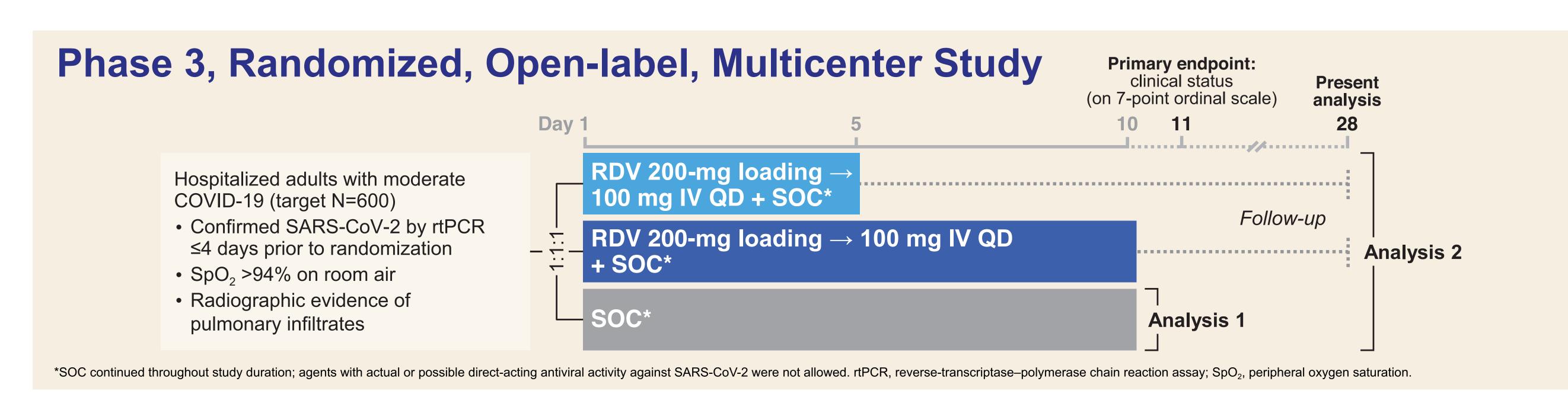
Introduction

♦ Remdesivir (RDV) is a broad-spectrum nucleotide analog prodrug that inhibits viral RNA polymerases, and has demonstrated potent in vitro and in vivo activity against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)[1-3]

♦ Results from the Phase 3 SIMPLE-Moderate study (GS-US-540-5774; NCT04292730) showed that hospitalized patients with COVID-19 not requiring O_2 support who were treated with 5 days of RDV had higher odds for improvement vs those treated with standard of care (SOC) at Day 11[4]

♦ The FDA Emergency Use Authorization for RDV was broadened to include hospitalized patients irrespective of O_2 support based on these data

Objective

♦ To assess predictors of clinical improvement at Day 28 in patients with moderate COVID-19 who were enrolled in the SIMPLE-Moderate Study

Methods

Phase 3, Randomized, Open-label, Multicenter Study

*SOC continued throughout study duration; agents with actual or possible direct-acting antiviral activity against SARS-CoV-2 were not allowed. rtPCR, reverse-transcriptase–polymerase chain reaction assay; SpO₂, peripheral oxygen saturation.

♦ Study enrolled from March 15 to April 18, 2020; date of final follow-up: May 20

♦ 105 hospitals in 12 countries: Asia (Hong Kong, Republic of Korea, Singapore, and Taiwan), Europe (France, Germany, Italy, Netherlands, Spain, Switzerland, and UK), and North America (USA)

♦ Key exclusion criteria:
– Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5x upper limit of normal; creatinine clearance <50 mL/min
– Use of any experimental treatment for COVID-19 ≤24 h prior to dosing
– Any requirement for invasive mechanical ventilation (IMV) at screening

♦ Analysis sets:
– Analysis 1: SOC alone
– Analysis 2: combined RDV treatment arms and SOC alone (adjusting for treatment)

♦ Endpoints:
– Percentage of patients with clinical improvement (≥2-point improvement in clinical status on ordinal scale or discharged alive) at Day 28
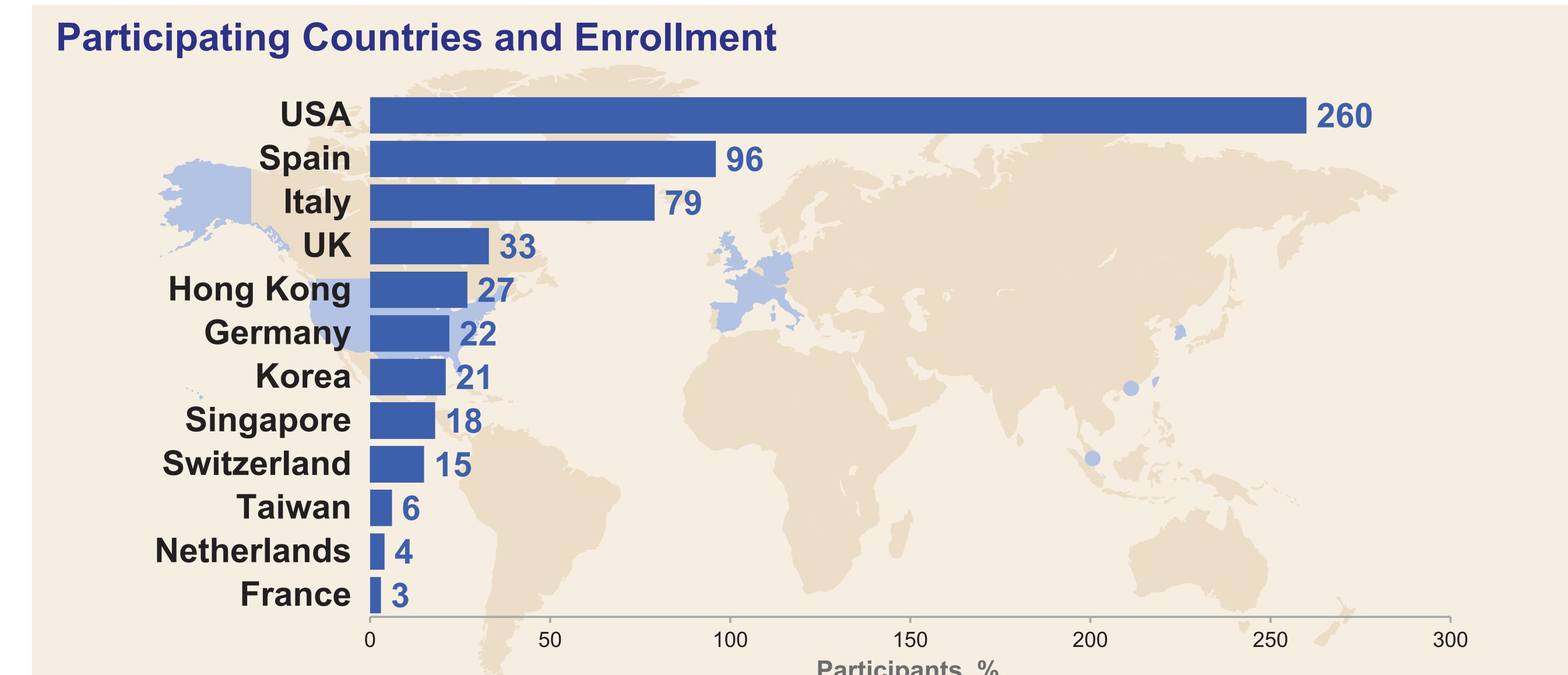– Mortality was not assessed as rates were low across groups

♦ Multivariate analysis:
– The final model included the variables automatically selected by stepwise logistic regression (p <0.05) from the following: age, sex, race, ethnicity, region, baseline clinical status, duration of hospitalization prior to study Day 1, duration of symptoms prior to study Day 1, baseline ALT, baseline AST, cardiovascular disease, hypertension, diabetes mellitus, asthma, and obesity
– Identified risk factors were adjusted by treatment effect in Analysis 2 with a multivariate logistic regression model
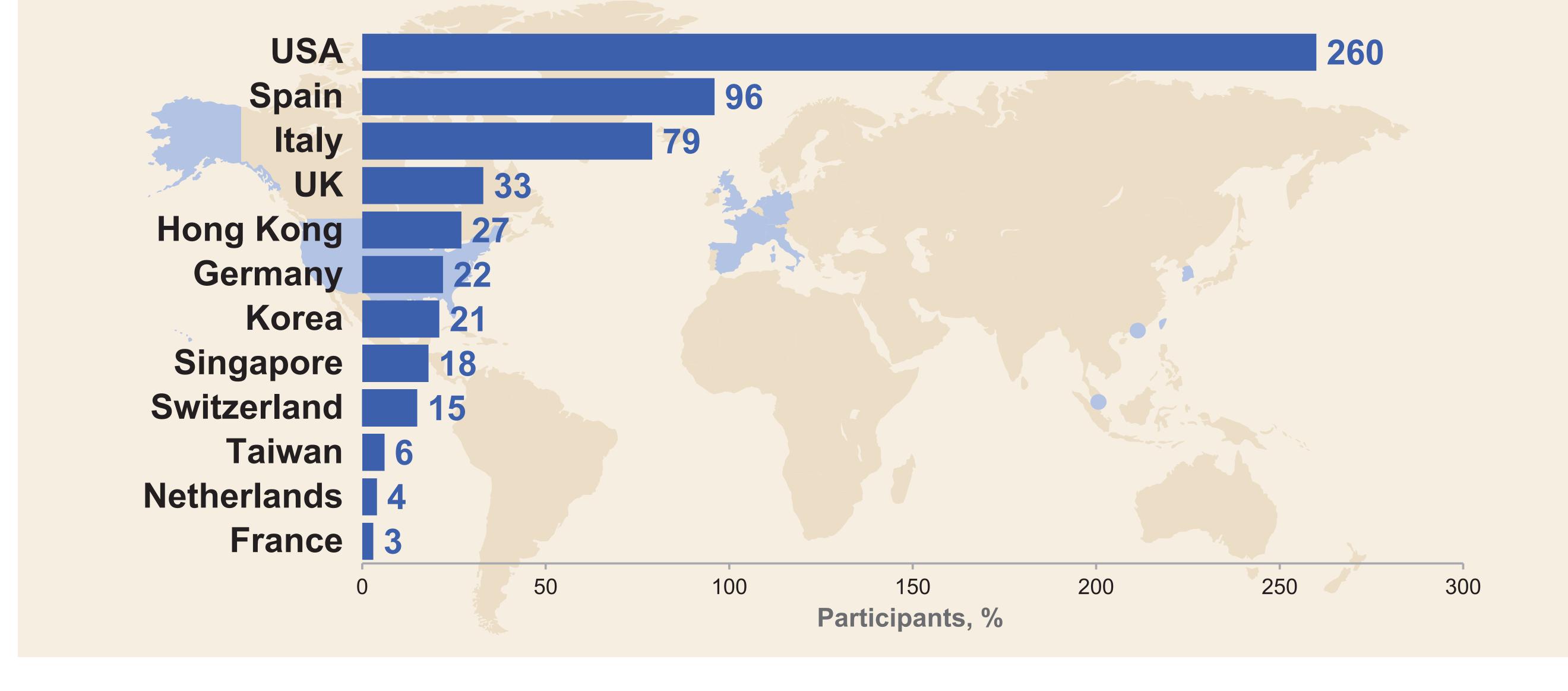
Clinical Outcomes Measured on 7-Point Ordinal Scale[4]

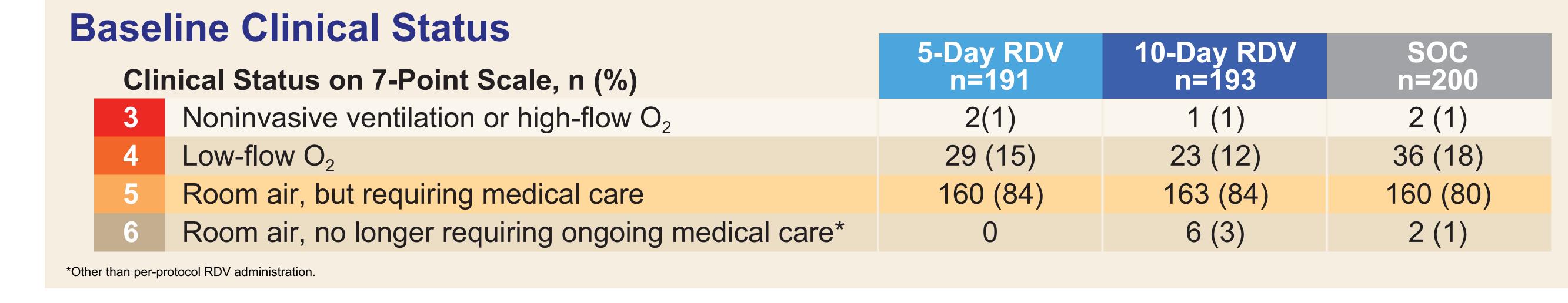|		
	1	Death
	2	IMV or ECMO
	3	Noninvasive ventilation or high-flow O_2
Hospitalized +	4	Low-flow O_2
	5	Room air, ongoing medical care (COVID-19 related or otherwise)
	6	Room air, no ongoing medical care (other than per-protocol RDV administration)
	7	Discharged

ECMO, extracorporeal membrane oxygenation.

Results

Participating Countries and Enrollment

Baseline Demographics and Characteristics

		5-Day RDV n=191	10-Day RDV n=193	SOC n=200
Median age, year (range)		58 (12–90)	56 (20–94)	57 (23–95)
Men, n (%)		114 (60)	118 (61)	125 (63)
Median BMI, kg/m² (range)		27 (17–77)	28 (16–63)	27 (16–54)
Region, n (%)	USA	76 (40)	99 (51)	85 (43)
	Rest of world	115 (60)	94 (49)	115 (57)
Race, n/n (%)	White	109/186 (59)	107/188 (57)	112/193 (58)
	Black*	35/186 (19)	37/188 (20)	27/193 (14)
	Asian	34/186 (18)	31/188 (16)	37/193 (19)
	Other†	8/186 (4)	13/188 (7)	17/193 (9)
Coexisting conditions, n (%)	Cardiovascular disease	111 (58)	111 (58)	107 (54)
	Hypertension	82 (43)	85 (44)	81 (41)
	Diabetes mellitus	71 (37)	85 (44)	76 (38)
	Asthma	22 (12)	31 (16)	28 (14)
	Obesity‡	53 (29)	59 (32)	55 (29)
Median duration of hospitalization before study Day 1, day (IQR)		2 (1, 3)	2 (1, 3)	2 (1, 3)
Median duration of symptoms before study Day 1, day (IQR)		8 (5, 11)	8 (5, 11)	9 (6, 11)

*33% (85/260) of all US patients; †Includes American Indian, Alaska Native, Native Hawaiian, Pacific Islander, and other; ‡Defined as body mass index (BMI) ≥30 kg/m²; percentages using numbers of patients with available baseline BMI as denominators. IQR, interquartile range.

Baseline Clinical Status

Clinical Status on 7-Point Scale, n (%)		5-Day RDV n=191	10-Day RDV n=193	SOC n=200
3	Noninvasive ventilation or high-flow O_2	2(1)	1 (1)	2 (1)
4	Low-flow O_2	29 (15)	23 (12)	36 (18)
5	Room air, but requiring medical care	160 (84)	163 (84)	160 (80)
6	Room air, no longer requiring ongoing medical care*	0	6 (3)	2 (1)

*Other than per-protocol RDV administration.

Clinical Improvement* From Baseline

*≥2-point improvement in clinical status or discharged alive.
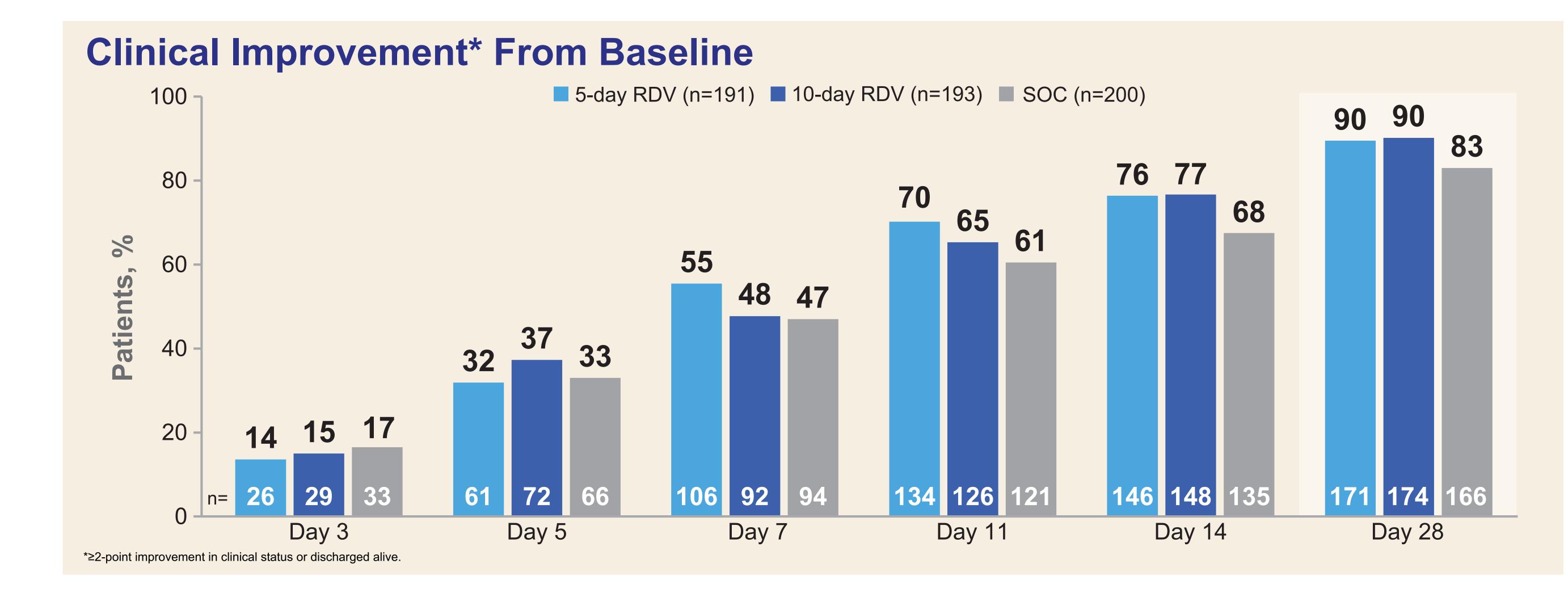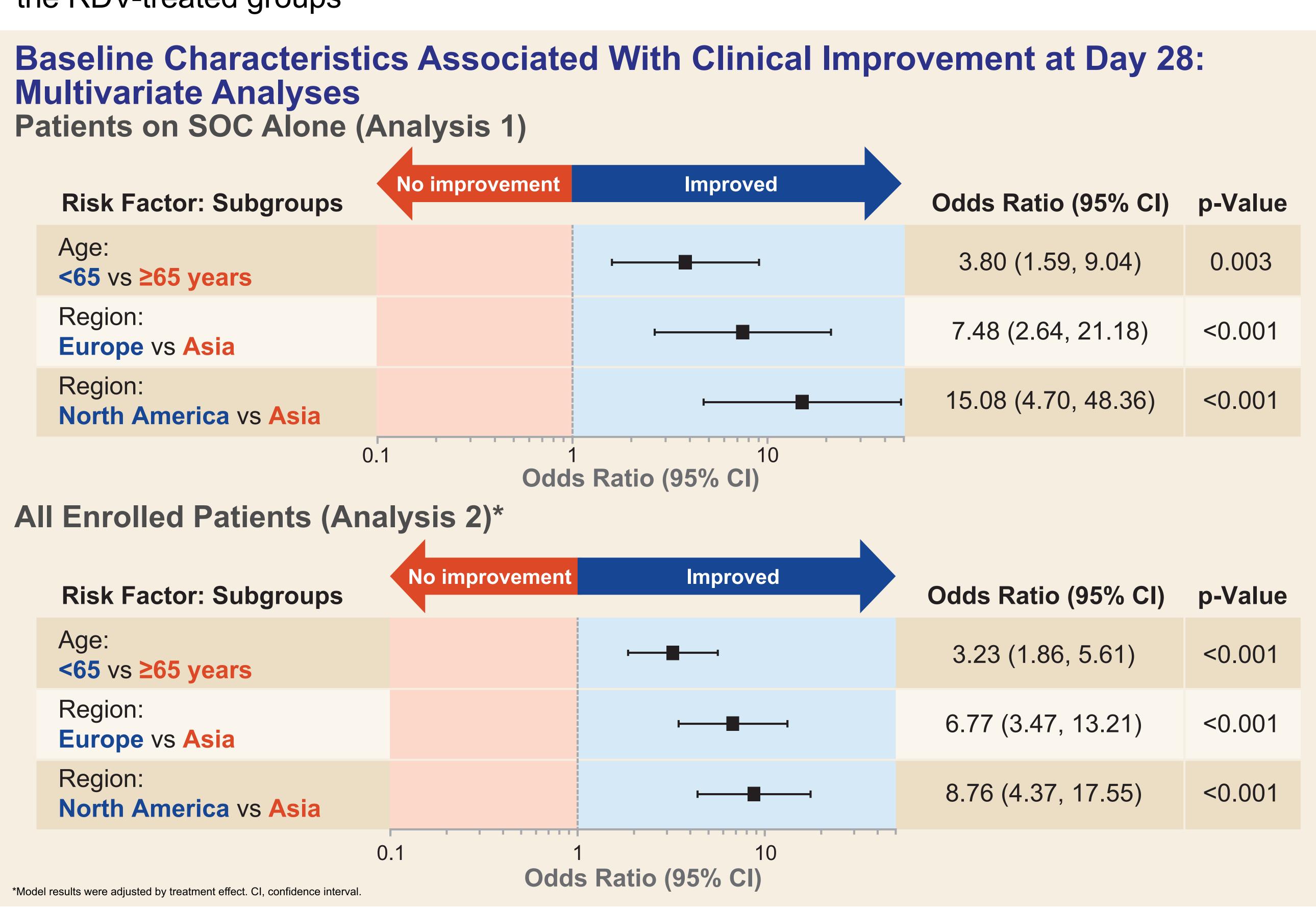
♦ Day 28 represents the analyzed time point for the regression model

♦ Most patients experienced clinical improvement by Day 28, with the highest rates observed in the RDV-treated groups

Baseline Characteristics Associated With Clinical Improvement at Day 28: Multivariate Analyses

Patients on SOC Alone (Analysis 1)

Risk Factor: Subgroups	Odds Ratio (95% CI)	p-Value
Age: <65 vs ≥65 years	3.80 (1.59, 9.04)	0.003
Region: Europe vs Asia	7.48 (2.64, 21.18)	<0.001
Region: North America vs Asia	15.08 (4.70, 48.36)	<0.001

All Enrolled Patients (Analysis 2)*

Risk Factor: Subgroups	Odds Ratio (95% CI)	p-Value
Age: <65 vs ≥65 years	3.23 (1.86, 5.61)	<0.001
Region: Europe vs Asia	6.77 (3.47, 13.21)	<0.001
Region: North America vs Asia	8.76 (4.37, 17.55)	<0.001

*Model results were adjusted by treatment effect. CI, confidence interval.

♦ After stepwise selection that considered all variables, age and region were the only variables to meet criteria for selection into the model for both analysis sets

♦ Age <65 years and non-Asian regions were associated with clinical improvement at Day 28 in both analysis sets

Conclusions

♦ In patients with moderate COVID-19, younger age and region (North America vs Asia; Europe vs Asia) were identified as significant prognostic factors for clinical improvement at Day 28

♦ These observations recapitulate younger age as a positive prognostic factor and highlight the differences in the impact of the pandemic globally

References: 1. Pizzorno A, et al. Antiviral Res 2020;181:104878; 2. Sheahan TP, et al. Sci Transl Med. 2017;9:eaal3653; 3. Williamson BN, et al. Nature 2020;585:273-6; 4. Spinner CD, et al. JAMA 2020 Aug 21;e2016349.