New Products

Nirsevimab (Beyfortus®): for RSV infection prevention

RSV-related hospitalizations decrease, but deaths increase

Supplementary Appendix

MedCheck Editorial team

September 15, 2024

Appendix 1

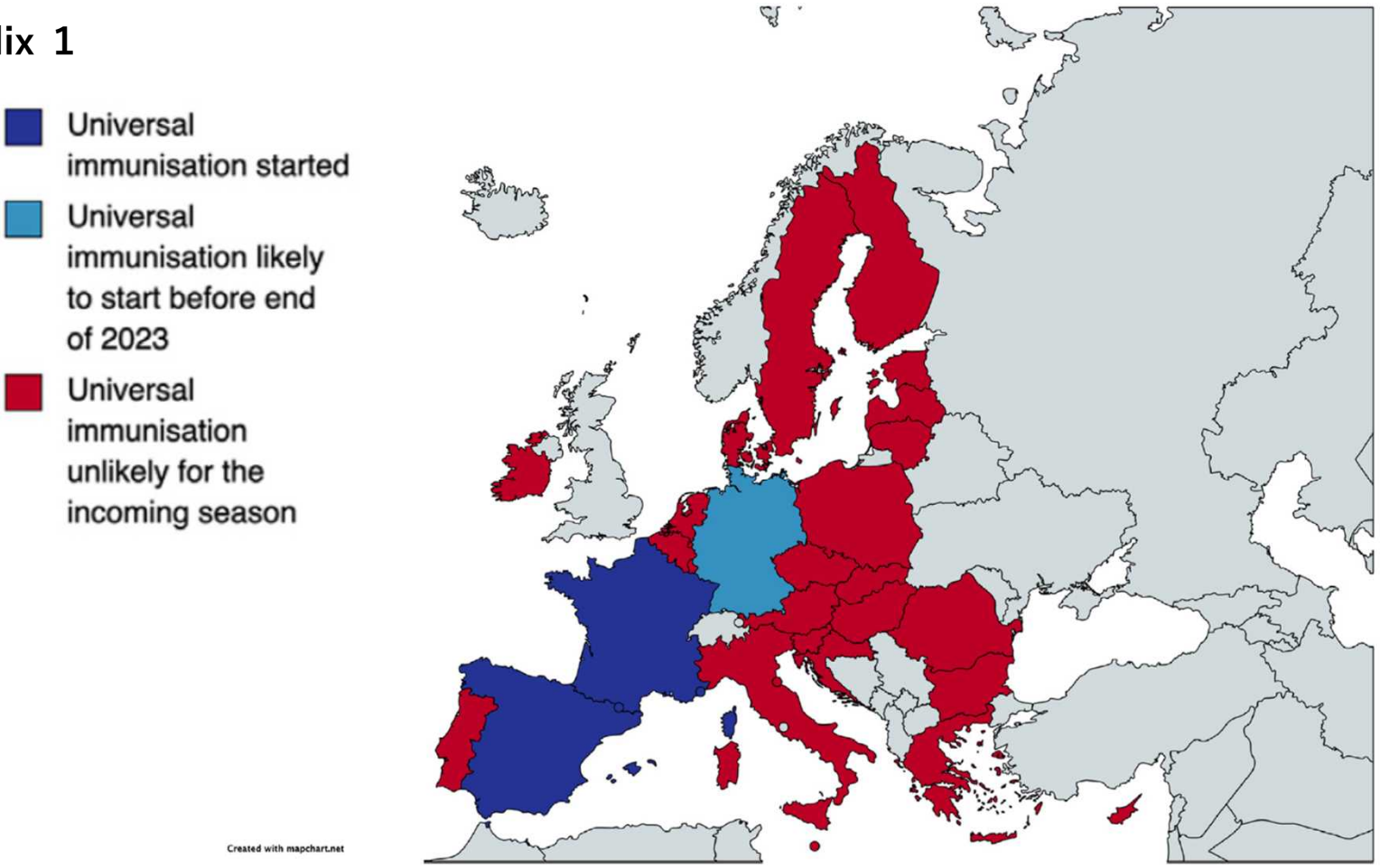
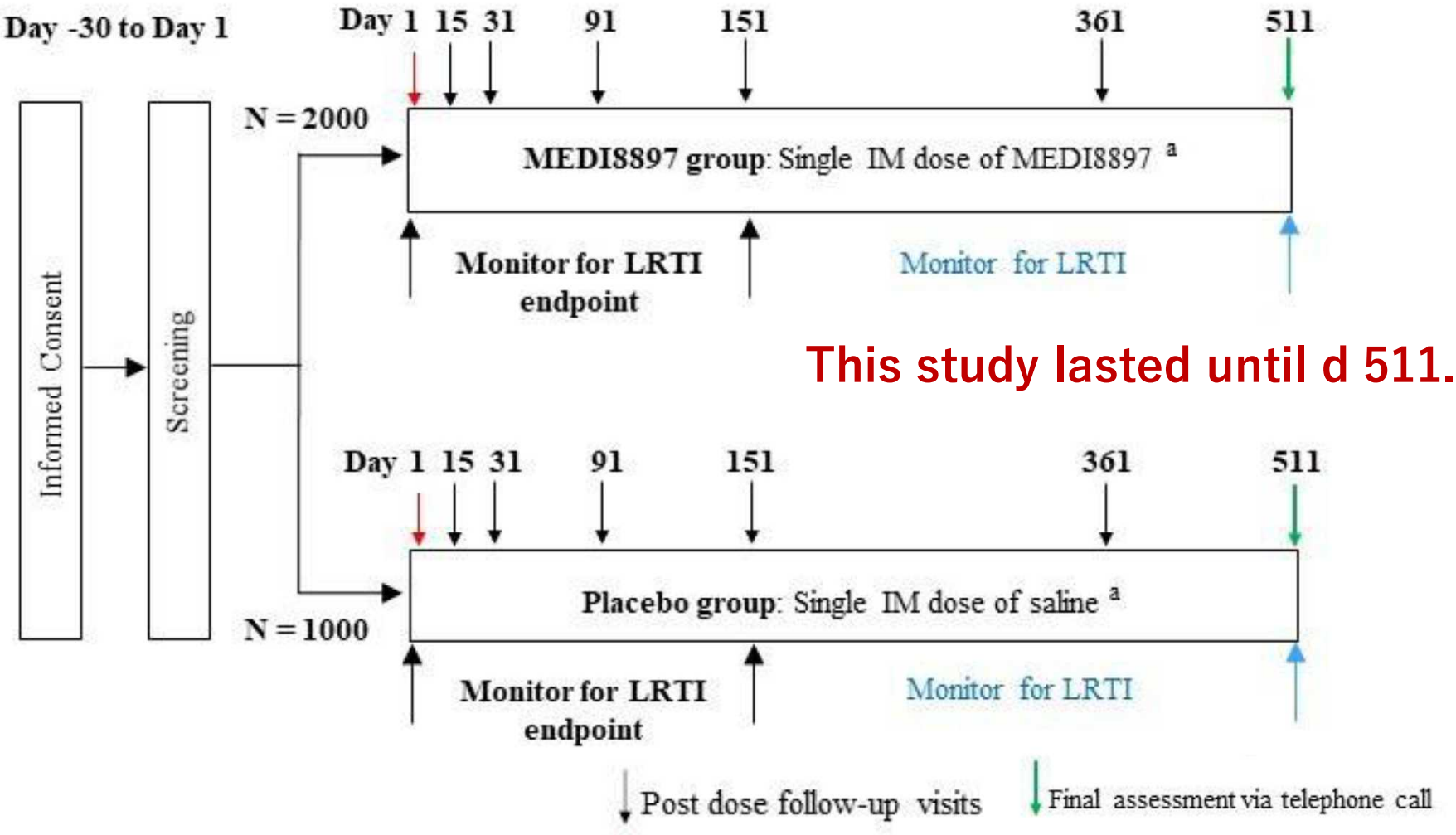


Fig. 1: **Diffusion of universal RSV immunisation in European Union countries**. Data obtained by contacting directly local clinical key opinion leaders or authorities (personal communications updated at October 3, 2023).

6) Luca DD et al. "Universal infant immunisation against respiratory syncytial virus and European inequalities: the pandemics lesson has not been learnt" Lancet Reg Health Eur. 2023 Oct 11:34:100753. doi: 10.1016/j.lanepe.2023.100753. eCollection 2023 Nov. PMID: 37927432

Appendix 2 : MELODY trial (from the protocol)

Figure 1 Study Flow Diagram

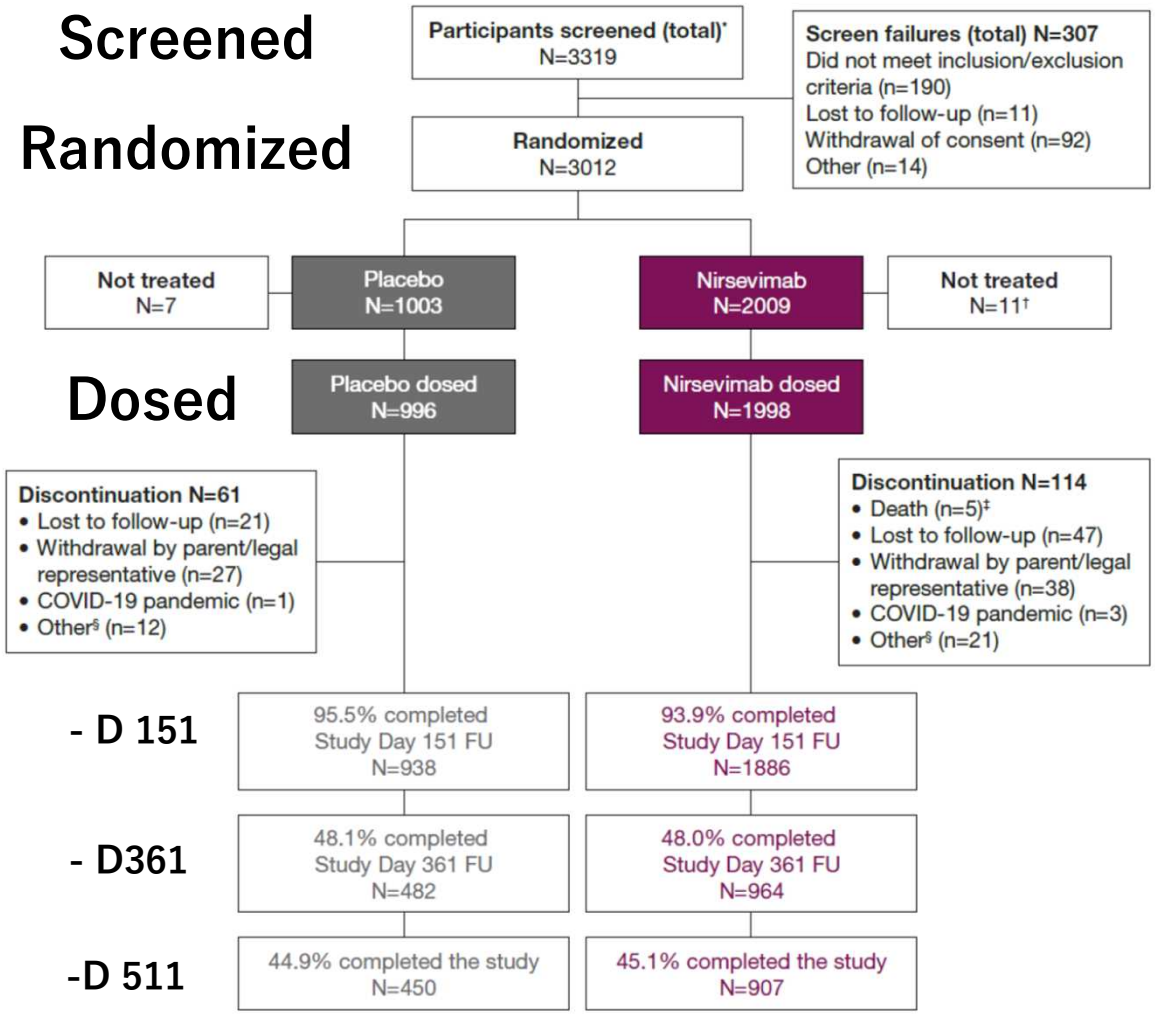


This study lasted until d 511.

Appendix 3 : MELODY trial, final report, Supplementary appendix

12) Muller WJ et al N Engl J Med 2023; 288 (16): 1533-1534 + supplementary appendix

12. Figure S1. Consort Diagram.



* Informed consent signed.

† **Includes 1 death in a randomized patient who never received IP.**

‡ **4 deaths occurred** post dosing through Study Day 361 and are included in the safety analysis of the full enrollment cohort; **1 death occurred after Study Day 361** (on **Day 440**) and is not included in the safety analysis.

§ Includes 1 participant who discontinued due to a nontreatment-emergent adverse event (IP not administered).

COVID-19, coronavirus disease 2019; FU, follow-up; IP, investigational product.

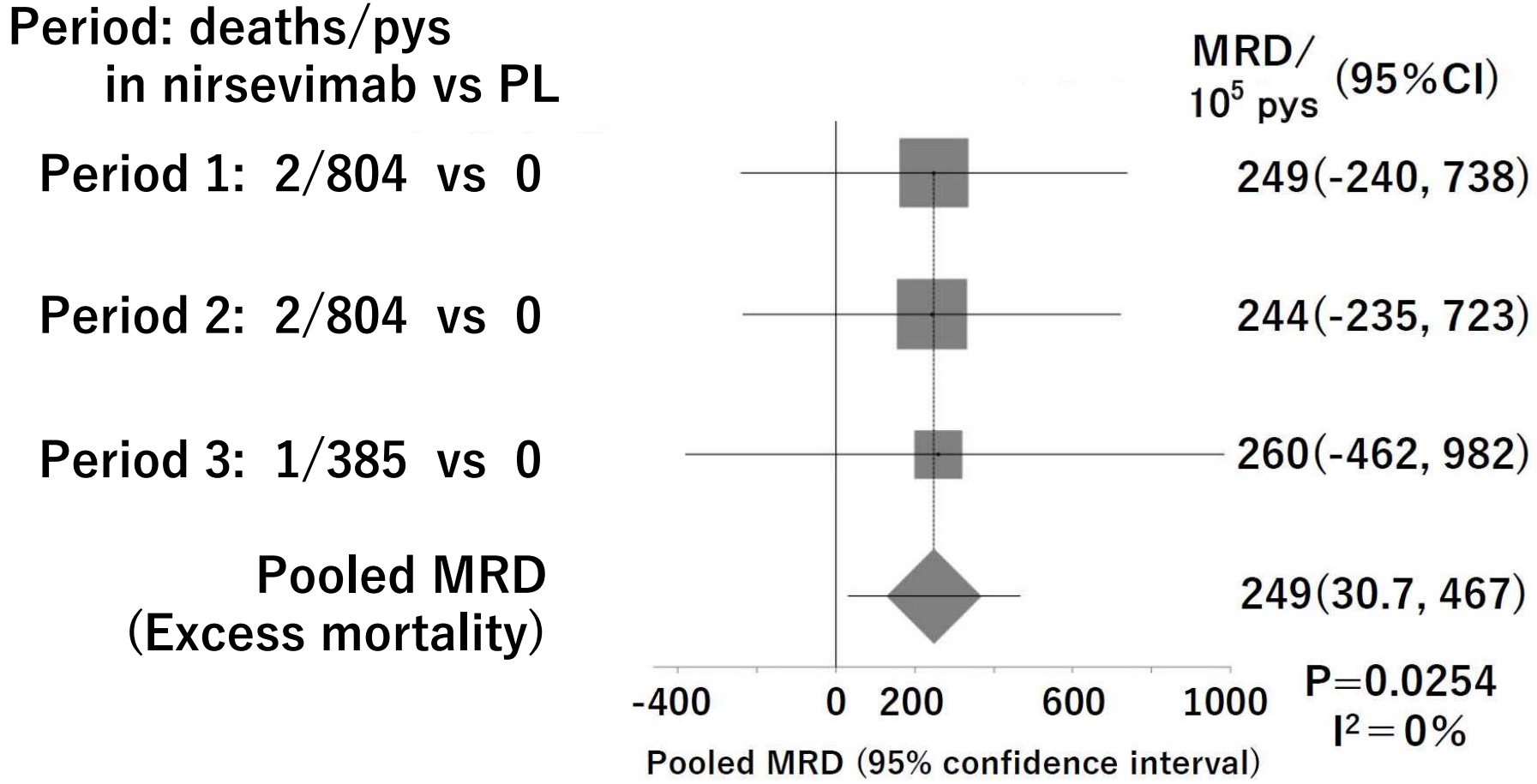
Appendix 4: Life table for MELODY trial

	Nirsevimab							
Days after dose	Number at start of interval	**Died during the interval**	Adjusted Number at risk	Adjusted Person-years at risk	Mortality rate /person-year	Survival rate /person-year	**Cumulative mortality Rate**	
							/py	**/10^5py**
0-150	1998	2	1943	804	0.00249	0.99751	0.00249	**249**
151-360	1886	2	1426	820	0.00244	0.99508	0.00492	**492**
361-511	964	1	936	385	0.00260	0.99249	0.00751	**751**
511	907							

	Placebo							
Days after dose	Number at start of interval	**Died during the interval**	Adjusted Number at risk	Adjusted Person-years at risk	Mortality rate /person-year	Survival rate /person-year	**Cumulative mortality Rate**	
							/py	**/10^5py**
0-150	996	0	967	400	0.000	1.00	0.000	**0**
151-360	938	0	710	408	0.000	1.00	0.000	**0**
361-511	482	0	466	192	0.000	1.00	0.000	**0**
511	450							

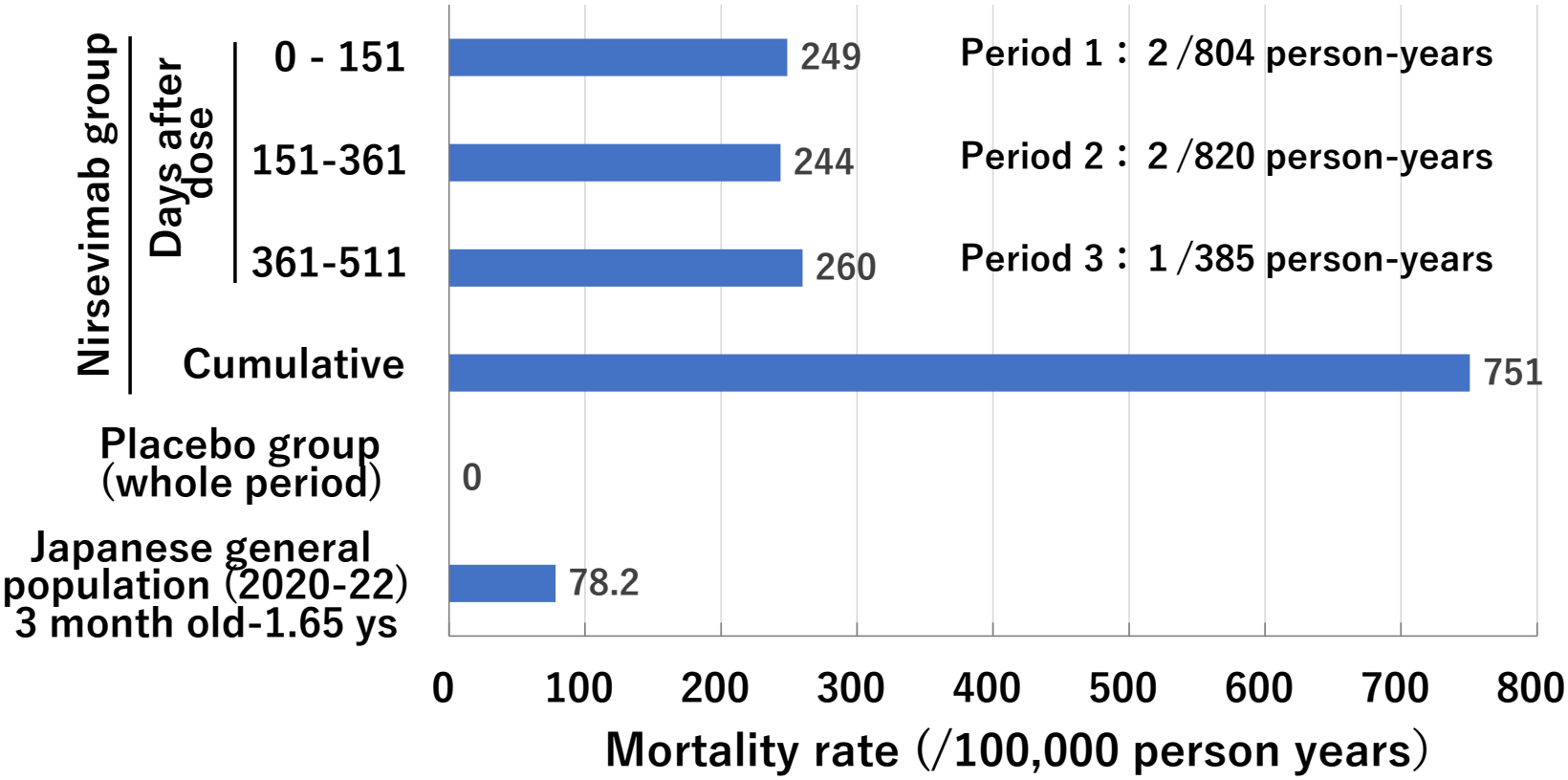
Created by MedCheck using data from 12) Muller WJ et al N Engl J Med 2023; 288 (16): 1533-1534 + supplementary appendix

Appendix 5 : Meta-analysis of mortality rate differences (MRD) by period in MELODY trial



Created by MedCheck using data from 12) Muller WJ et al N Engl J Med 2023; 288 (16): 1533-1534 + supplementary appendix

Appendix 6 : Mortality rate by period and cumulative mortality rate in MELODY trial



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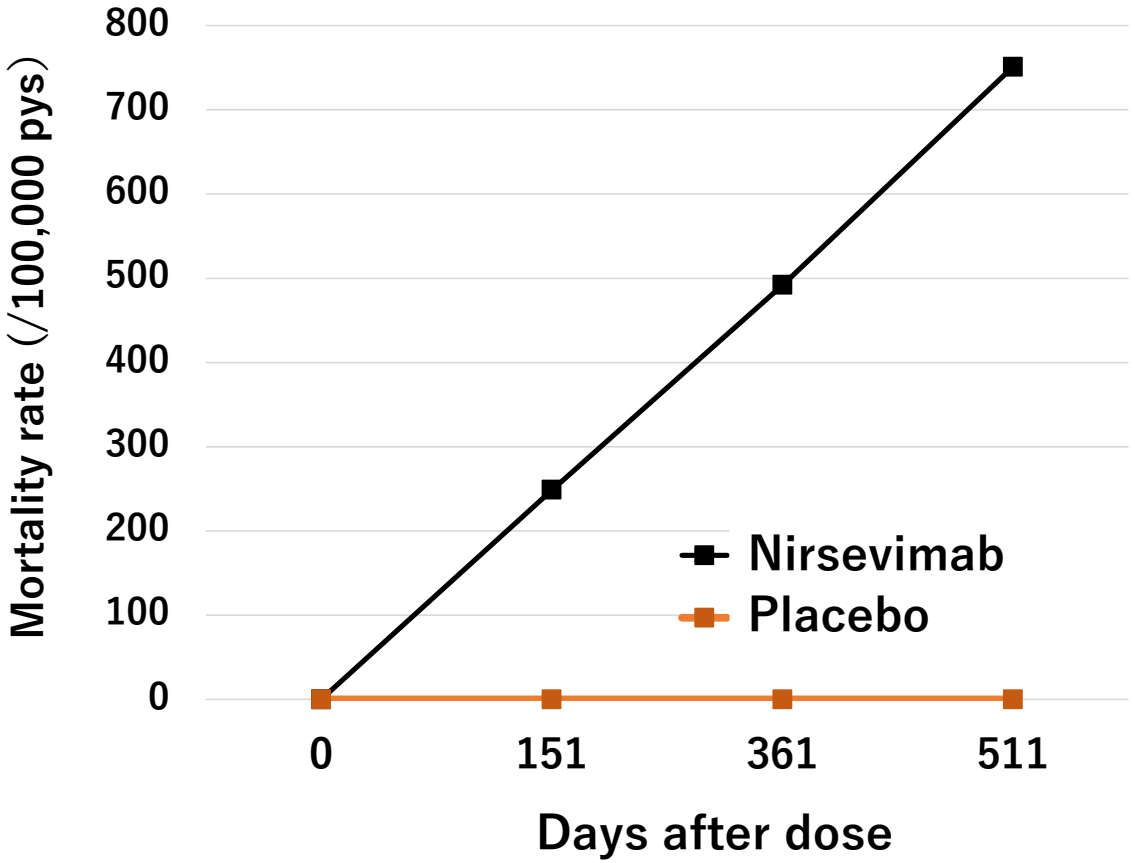
Appendix 6 ： Cumulative mortality rate of MELODY trial



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Appendix 8 :

Infant mortality rate of general population for the same age as MELODY trial

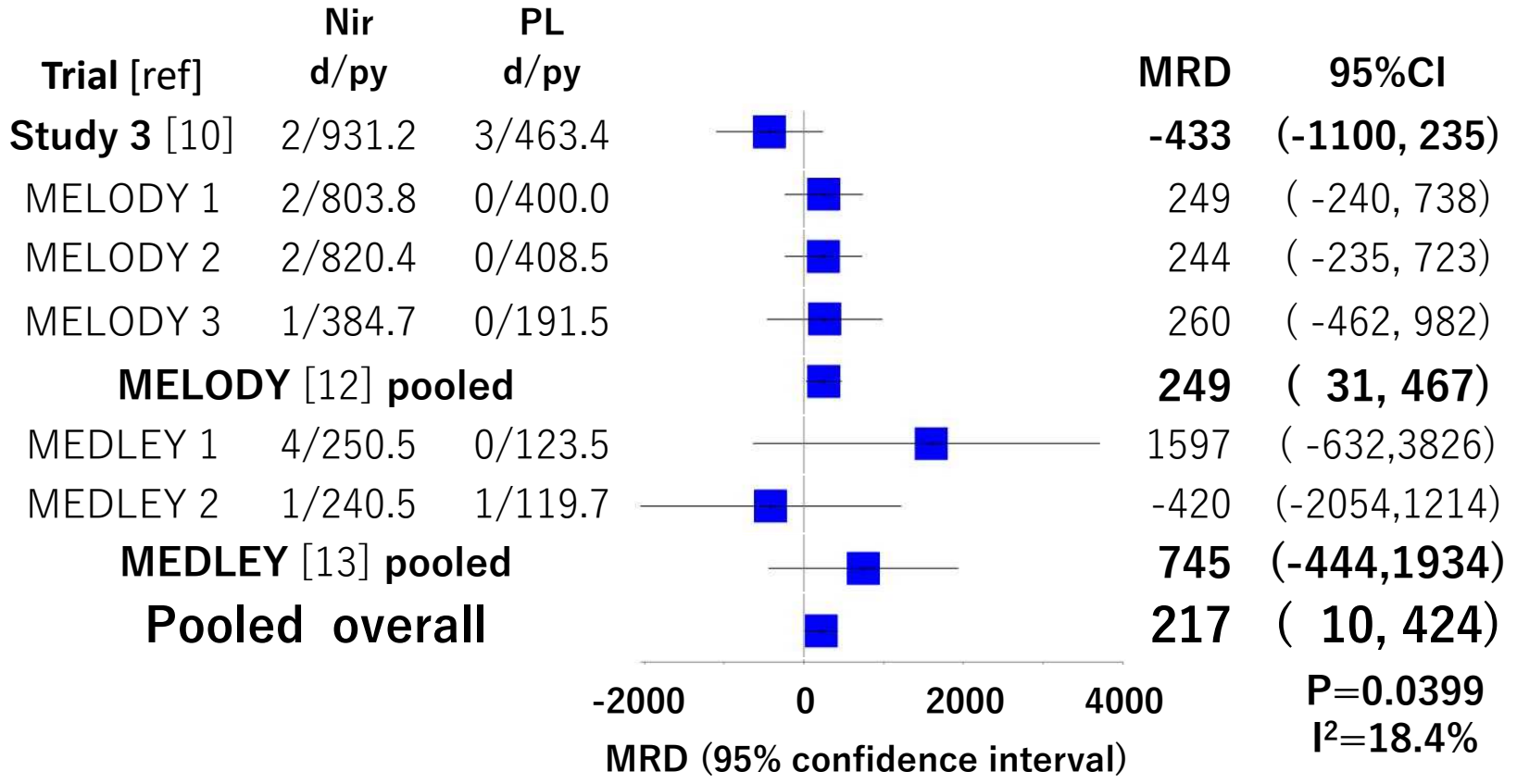
The average age at the start of the MELODY trial was 3 months (0.25 years), and the end of the trial was day 511 when the average age of the participants was estimated 1.65 years (0.25+1.4). So the mortality rate (MR) in the Japanese general population between 3 months to 1.65 years was estimated from the Japanese vital statistics:
https://www.e-stat.go.jp/egeneral n/stat-search/files?page=1&toukei=00450011&tstat=000001028897

1. MR for 0 years (average of 2020 to 2022) was 176.0/100,000 peason-years(/10^5pys) (Japan)
2. MR for 3-11 months was 62.4/105pys
3. MR for 1 year to 1.65 years (after 1.4 years since 3 months) was 15.8/10^5pys
   MR of 1 year age (12 months to less than 2 years) children (24.5/10^5pys) x 0.65 = 15.8/10^5pys
4. Estimated MR between 3 months and 511 days = 62.4 + 15.8 = 78.2/10^5pys
5. Using the European infant mortality rate (E_0), the mortality rate between 3 months and 511 days (E_1) was estimated as $E_1 = E_0 \times 78.2/176.0$ （/10^5pys).
6. According to https://ec.europa.eu/eurostat/databrowser/view/demo_minfind/default/table?lang=en

Average mortality rate of infants aged 0 years in the EU are 3.20/1000pys→ E_1:142/105pys
Spain 2.6/1000pys →E_1: 116/10^5pys. Turkey(the highest) 9.2/1000pys →E_1: 409/10^5pys.
Cumulative mortality rate (751/10^5pys) in MELODY trial is higher than that of any countries.

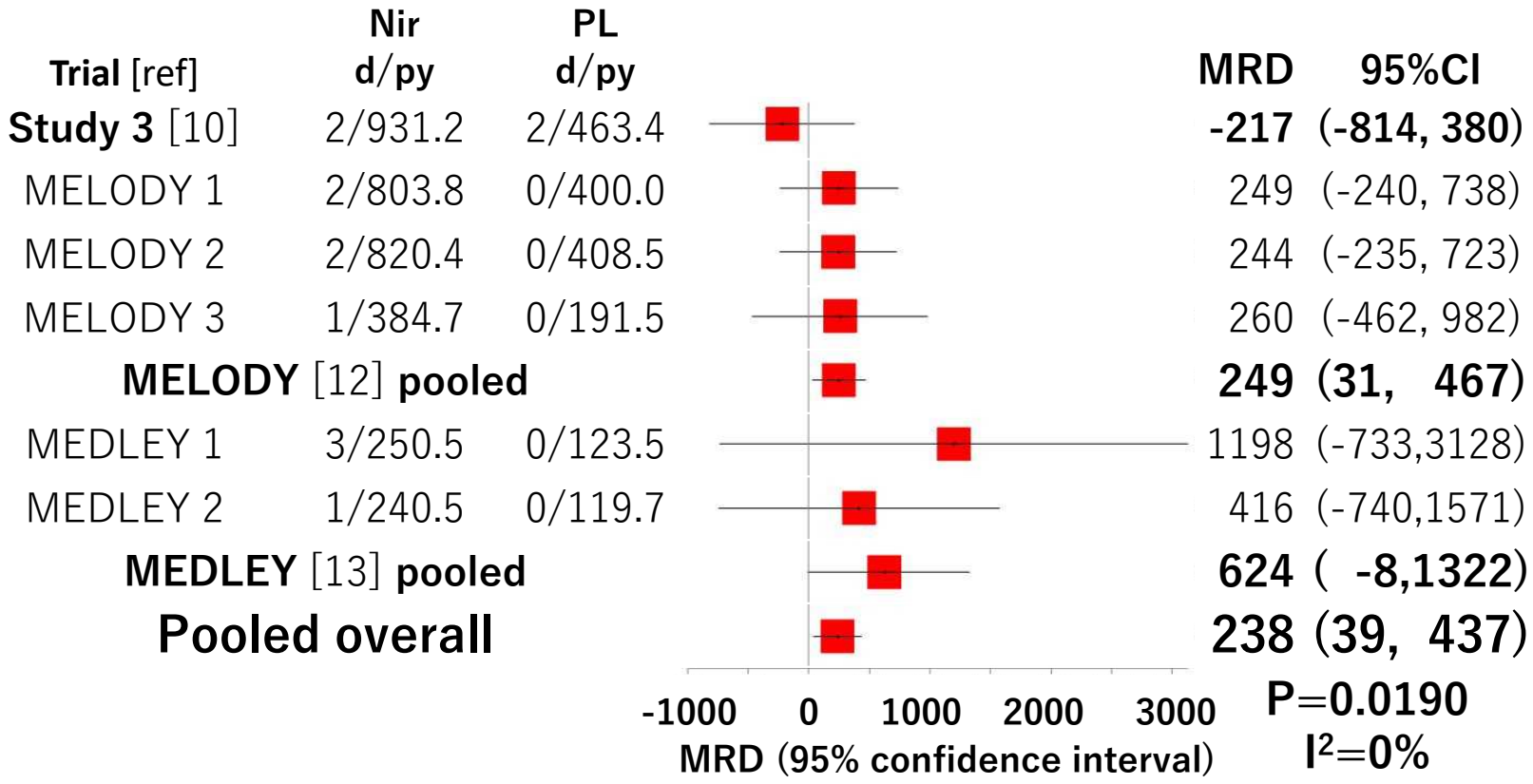
Figure 1：

All-cause mortality rate differences in three pivotal RCTs of nirsevimab: meta-analysis



Nir: nirsevimab, PL: placebo, d: number died, py: person-years, MRD: mortality rate difference, 95%CI: 95% confidence interval, All pooled MRD were calculated as Fixed effects by StatsDirect 3.3.6. P value for pooled MELODY trial was 0.0254 (I^2=0%), P value for pooled MEDLEY trial was 0.2197 (I^2=62.9%). Created by MedCheck using data from 3 pivotal RCTs of nirsevimab [10-13].

Figure 2：
Non-RSV-related mortality rate differences in three pivotal RCTs of nirsevimab: meta-analysis



Nir: nirsevimab, PL: placebo, d: number died, py: person-years, MRD: mortality rate difference, 95%CI: 95% confidence interval, All pooled MRD were calculated as Fixed effects by StatsDirect 3.3.6. P value for pooled MELODY trial was 0.0254 (I^2=0%), P value for pooled MEDLEY trial was 0.0802 (I^2=0%). Created by MedCheck using data from 3 pivotal RCTs of nirsevimab [10-13].

Table: Causes of death in the three pivotal RCTs of nirsevimab

Trial name Subjects	Nirsevimab group: Number of participants	Control group: Number of participants
Study 3 Preterm	Nirsevimab：968	Placebo：479
	Death	Pericarditis
	Pulmonary vein stenosis	Bacterial pneumonia
		RSV-pneumonia
MELODY Term, healthy	Nirsevimab：1998	Placebo：996
	cause unknown＊	None
	acute gastroenteritis (could be ischemic gastroenteritis)	
	acute gastroenteritis (could be ischemic gastroenteritis)	
	Skul fracture （automobile accident）	
	cause unknown	
MEDLEY Preterm or high-risk (CHD or CLD)	Nirsevimab：614	Palivizumab：304
	SUD with CHD (VSD+ASD etc)	*Bronchiolitis*
	SUD in pumonary atresia with VSD	
	Cardiogenic shock with heart failure due to VSD+ASD	
	Cardiopulmonary failure, secondary to acute bronchiolitis	
	SARS-CoV-2 pneumonia	

＊：the investigator suspected undiagnosed metabolic disease but the infant died of an unknown cause.
The cause of death for black (italic) could be due to RSV infection if RSV testing was not performed.
Red (Bold) indicates the cause unknown or sudden unexpected death (SUD) or cardiovascular death.
Blue (Bold) indicates the other non-RSV-related death, but “acute gastroenteritis” could be ischemic gastroenteritis