

ESM Table 1: Amendments summarized

Amendments	Modifications	Ethics Committee approval	ANSM authorization
		Date	Date
Amendment 1	1/ Increase in follow-up time to 12 months and inclusion time from 12 to 24 months 2/ Protocol clarification, including : - The dose of treatment administered for patients whose BMI for age is < 3° or > 97° percentile - The data collected between D2 and D5 (including PELOD2, Goldstein criteria and CVI that are collected daily from D2 to D5 and not only at D2 and D5) - The nature of the protocol deviations that will be used in the decision making regarding the conduct of the efficacy study were specified. - The name of the engineer responsible for the analysis has been changed	15/12/2015	18/12/2015
Amendment 2	1/ Addition of Kawasaki disease as a non-inclusion criterion. 2/ For those wrongly included (for bacteriological reason), patients should only be considered wrongly included if the germ is not found in suspected streptococcal shock (not for staphylococcal shock, as in the CDC criteria) 3/ In the selection criteria, change concerning the filling criterion: - For patients under 12 years: keep 40 ml/kg - For patients aged 12 years and over: 30 ml/kg (which corresponds to the Surviving Sepsis Campaign criteria for adults) Change of the fluid bolus time from 1 hour to 3 hours, as in CDC criteria. 4/ Clarification: administration of treatment within 12 hours of the onset of the first signs of shock or PICU admission is a "recommendation" (the criterion for non-inclusion being that the first signs of shock should not have occurred for more than 24 hours). 5/ The addition of a 1-year visit (including AEs, SAE, mortality, POPC score, GOS-E Peds scale).	29/03/2016	25/04/2016
Amendment 3	1/ Increase in the duration of inclusions by 12 months (24 months to 36 months) 2/ Modification of the list of investigators 3/ PCOC score no more collected at 1-year	03/01/2017	NA
Amendment 4	Increase in duration inclusion (36 months to 38 months) and the number of patients to be included (20 to 30)	19/12/2017	NA
Amendment 5	Increase in duration of inclusions (38 months to 41 months)	27/02/2018	NA

AE: Adverse Event; CPP: French research ethics committees; ANSM: French National Agency for Medicines and Health Products Safety (Agence Nationale de la Sécurité du Médicament); BMI: Body Mass Index; CDC: Centre for Disease Control and prevention; CVI: Cumulative Vasopressor Index; PELOD: Pediatric Logistic Organ Dysfunction, POPC: Pediatric Overall Performance Category; GOS-E: Glasgow Outcome Score Extended.

ESM Table 2: Infectious gateway

	Control group	IVIG group
Vagina, N (%)	2 (14.3)	2 (18.2)
Upper respiratory tract N (%)	3 (21.4)	5 (45.5)
Lower respiratory tract including pleura N (%)	6 (42.9)	0 (0)
Cutaneous	3 (21.4)	3 (27.3)
Of which chickenpox N (%)	1 (33.3)	1 (33.3)
Articular N (%)	0 (0)	1 (9.1)

IVIG: intravenous immunoglobulin.

Values are numbers (N) with %.

The control group consists of patients treated with Albumin 4%.

ESM Table 3: Time course of hemodynamic parameters during the first five days according to the allocated group

	Admission (Day 1)		Day 2		Day 3		Day 4		Day 5	
	Control	IVIG	Control	IVIG	Control	IVIG	Control	IVIG	Control	IVIG
Hypotension adjusted for age Yes : N (%) MD : N	8 (53.3) 0	10 (66.7) 0	8 (57.1) 1	10 (71.4) 1	-	-	-	-	3 (25.0) 3	2 (33.3) 9
Minimal blood pressure	n=15 84 [71-103]	n=15 84 [67-89]	n=14 83 [79-92]	n=14 81 [71-96]	-	-	-	-	n=12 98 [91-102]	n=6 94 [84-99]
SBP (mmHg) Med [Q1-Q3]	42 [36-53]	43 [34-47]	47 [42-54]	50 [41-54]	-	-	-	-	56 [50-59]	59 [55-72]
DBP (mmHg) Med [Q1-Q3]										
Lactate (mmol/L) Maximal value	n=15 2.8 [2.3-3.6]	n=15 3.4 [2.4-4.3]	n=13 1.5 [1.2-3.0]	n=14 1.4 [1.0-3.2]	n=11 1.4 [0.8-2.4]	n=11 1.5 [1.0-2.0]	n=9 1.3 [0.7-2.1]	n=9 1.9 [1.3-2.0]	n=9 1.5 [1.2-2.0]	n=3 1.9 [1.4-2.4]
Lactate clearance Med [Q1-Q3]	-	-	-1.10 [-1.4 - -0.5]	-1.2 [-3.0 - -0.4]	-	-	-	-		
Diuresis (ml/kg/h) Med [Q1-Q3]	n=15 1.7 [1.3 -2.6]	n=14 1.9 [1.3-2.3]	n=15 2.2 [1.2-2.8]	n=12 1.7 [1.2-2.1]	-	-	-	-	n=7 1.5 [0.7-4.3]	n=5 4.1 [2.7-4.5]
Fluid volume bolus (ml/kg) Med [Q1-Q3]	n=15 60 [40-80]	n=15 48 [20-80]	n=1 20 [20-20]	n=2 28 [26-30]	n=2 15 [10-20]	n=2 15,5 [10-21]	n=0 -	n=1 23,5 [23,5-23,5]	n=1 9 [9-9]	n=0 -
CVI Med [Q1-Q3]	n=15 4 [4-4]	n=15 4 [4-4]	n=15 4 [3-4]	n=15 4 [0-4]	n=15 4 [0-4]	n=15 4 [0-0]	n=14 0 [0-0]	n=15 0 [0-0]	n=13 0 [0-0]	n=13 0 [0-0]

The control group consists of patients treated with albumin 4%.

Values are Median (Med) with interquartile [Q1-Q3] or Numbers (N) with %. MD: Missing Data

IVIG: intravenous immunoglobulins; CVI: cumulative vasopressor index; DBP: diastolic blood pressure, SBP: systolic blood pressure

ESM Table 4: Biological data during the first five days in PICU according to allocated group

	Admission		Day 2		Day 3		Day 4		Day 5	
	Control	IVIG	Control	IVIG	Control	IVIG	Control	IVIG	Control	IVIG
PCT Maximal value ($\mu\text{mol/L}$) Med [Q1-Q3]	n=9 71 [60-100]	n=12 88 [50 -230]	n=10 25 [15-71]	n=10 137 [99 -261]	NA	NA	NA	NA	n=6 6 [3-9]	n=6 9 [2 -19]
pH Minimal value	n=15 7.3 [7.2-7.4]	n=15 7.3 [7.2-7.4]	n=15 7.4 [7.3-7.4]	n=14 7.4 [7.2-7.4]	NA	NA	NA	NA	n=9 7.4 [7.4-7.5]	n=6 7.44 [7.4-7.5]
Na (mmol/L) Minimal value	n=15 134 [132-137]	n=15 134 [130-138]	n=15 138 [136-141]	n=15 137 [134-139]	NA	NA	NA	NA	n=9 142[138-148]	n=6 138 [137-143]
Bicarbonates (mmol/L) Minimal value	n=15 17 [15-18]	n=15 16 [13-19]	n=15 19 [17-23]	n=14 20 [17-22]	NA	NA	NA	NA	n=8 24. [23-27]	n=5 29 [28-29]
Urea (mmol/L) Maximal value	n=15 12.9 [6.9-14.9]	n=15 11 [5.3- 17.9]	n=15 4.9 [3.5-11.7]	n=14 .6.0 [3.6-9.0]	NA	NA	NA	NA	n=8 6.2 [2.7-8.7]	n=6 4.4 [2.5-7.4]
Creatinine ($\mu\text{mol/L}$) Maximal value	n=15 115 [39-147]	n=15 79 [53-184]	n=15 59 [38-104]	n=15 52 [40-65]	n=12 52. [35-75]	n=11 44 [35-50]	n=11 44 [26-71]	n=9 40 [36-44]	n=8 42 [28-66.]	n=6 34. [18-41]
ASAT (UI/L) Maximal value	n=15 56 [41-82]	n=15 77 [52-113]	n=13 43 [28-74]	n=14 71 [42-93]	n=8 58 [30-115]	n=8 78 [67-265]	n=6 69 [67-85]	n=8 111 [49 -1038]	n=7 64 [35-69]	n=4 56. [41-2956]
ALAT (UI/L) Maximal value	n=15 38 [19-80]	n=15 53 [34-81]	n=13 39 [23-62]	n=14 54 [35-76]	n=8 46 [31-94]	n=8 73 [55-156]	n=6 64 [42-77]	n=7 71 [57-176]	n=7 57 [23-74]	n=4 55 [50-802]
CK (UI/L) Maximal value	n=13 336 [67-775]	n=13 387 [295-1283]	n=11 190 [54-1382]	n=11 812 [282-1910]	NA	NA	NA	NA	n=4 223 [107-496]	n=3 158 [41-278]
Total bilirubine (mmol/L) Maximal value	n=13 11 [10-19]	n=15 13 [7-27]	n=10 11. [9-14]	n=13 8 [7-10]	n=7 10 [7-12]	n=5 9 [3-11]	n=6 10. [7-46]	n=6 5 [5-73]	n=7 13 [6-37]	n=3 5 [3-62]

Platelets (G/L) Minimal value	n=15 96 [74-155]	n=15 115 [94-143]	n=15 84 [42-220]	n=15 88 [78-121]	n=10 54. [31-76]	n=11 88 [62-94]	n=8 57. [41.-107]	n=9 62 [60-126]	n=9 130 [55-203]	n=6 97 [27-142]
White blood cells (G/L) Minimal value	n=15 11.1 [8.1-16.1]	n=15 10.6 [6.6-12.7]	n=15 14.4 [12.1-34.6]	n=14 9.7 [5.7-17.7]	n=10 14.2 [12.3-.18.3]	n=11 14.4 [6.3-35.5]	n=8 18.1 [13.7-23.6]	n=9 14.1 [10.0-22.1]	n=9 18.6 [17.1-23.6]	n=6 19.1 [10.8-30.2]
Hemoglobin (g/L) Minimal value	n=15 105 [100-117]	n=15 107 [99-110]	n=15 102 [94-110]	n=15 98 [93-108]	NA	NA	NA	NA	n=9 101 [95-114]	n=6 96. [90-110]
Lymphocytes Minimal count (G/L)	n=11 0.4 [0.2-1.3]	n=14 0.4 [0.3-0.7]	n=12 1.9 [0.9-5.5]	n=13 1.2 [0.6-2.1]	n=7 3.9 [1.8-4.8]	n=9 1.9 [1.1-2.5]	n=4 8.5 [4.7-10.5]	n=8 3.2 [2.8-3.9]	n=6 7.0 [6.0-8.5]	n=5 4.2 [2.9-4.9]
APTT (s) Maximal value	n=13 41.8 [35.0-49.6]	n=14 46.5 [35.0-53.4]	n=13 41.8[35.7-44.6]	n=12 41.9 [31.2-.46.9]	NA	NA	NA	NA	n=7 31.9 [30.0-33.2]	n=4 34.4 [29.4-78.0]
PT (%) Minimal value	n=15 60 [51-73]	n=15 47 [29-65]	n=14 69. [55-86]	n=12 79. [60.-92.]	NA	NA	NA	NA	n=8 80 [65-90]	n=3 96 [77-100]
INR Maximal value	n=12 1.5 [1.3-2.1]	n=9 2.1 [1.7-2.5]	n=11 1.2 [1.1-1.4]	n=7 1.3 [1.1-1.7]	NA	NA	NA	NA	n=4 1.1 [1.1-1.1]	n=3 1.0 [1.0-1.2]
Fibrinogen (G/L) Minimal value	n=15 4.9 [2.9-5.5]	n=15 3.4 [2.6-4.3]	n=14 4.1 [3.6-4.4]	n=14 3.6 [2.6-4.3]	NA	NA	NA	NA	n=7 3.4 [3.1-4.9]	n=4 1.9 [1.8-2.8]
Immunoglobulin G	n=13 6.4 [5.5-7.1]	n=13 6.1 [5.4-7.1]	n=0	n=0	n=9 6.9 [6.2-8.6]	n=6 19.2 [17.8-20.9]	n=0	n=3 15.8 [14.7-19.8]	n=3 8.9 [5.3-13.5]	n=0
Immunoglobulin A	n=13 0.9 [0.6-1.2]	n=13 0.7 [0.5-0.9]	n=0	n=0	n=9 1.4 [1.2-1.5]	n=6 0.8 [0.7-0.8]	n=0	n=3 0.8 [0.4-1.3]	n=3 1.1 [1.1-2.6]	n=0
Immunoglobulin M	n=13 0.7 [0.5-1.1]	n=13 0.7 [0.5-0.9]	n=0	n=0	n=9 1.0 [0.9-1.6]	n=6 0.6 [0.5-0.6]	n=0	n=3 1.4 [0.8-1.8]	n=3 1.3 [1-2.6]	n=0

The control group consists of patients treated by albumin 4%. Values are Median (Med) with interquartile [Q1-Q3] or Numbers (N) with %. MD: Missing Data

ALAT: alanine aminotransferase; ASAT: aspartate aminotransferase, APTT: activated partial thromboplastin time, CK: creatin kinase; INR: international normalized ratio, PCT: procalcitonin; PT: prothrombine time, NA: not applicable

ESM Table 5: Support care in each treatment arm

	Control	IVIG
PICU length of stay (days) Mean (Min-Max)	5.7 (2-14)	7.7 (1-32)
Hospital length of stay (days) N=27 Mean (Min-Max)	17 (4-64)	9.3 (2-16)
Ventilation duration (days) Mean (Min-Max)	3.2 (1-7)	7.1 (3-17)
Days with Central Venous Catheter (days) Mean (Min-Max)	4.7 (0-15)	5.0 (0-33)
Urinary catheter (days) Mean (Min-Max)	3.7 (0-8)	2.7 (0-10)
Initial Antibiotics N (%)		
• Bêta-lactam	15 (100)	14 (93.3)
Yes Bêta-lactam AND lincosamid	15 (100)	14 (93.3)
Yes Lincosamid alone	0 (0)	1 (6.7)
Renal Replacement Therapy Yes N (%)	0 (0)	2 (13.3)
Chirurgical care Yes N (%)	3 (20)	0 (0)
ECMO Yes N (%)	0 (0)	1 (6.7)

The control group consists of patients treated by albumin 4%

Values are Mean (Min-Max) or Numbers (N) with %.

ECMO: extracorporeal membrane oxygenation, PICU: pediatric intensive care unit.

ESM Table 6: Number of subjects needed (per group) for a relative risk ranging from 0.40 to 0.80 and a proportion of events in the control group ranging from 23% to 29%

Pearson Chi-square Test is used for proportion difference

Fixed Scenario Elements	
Distribution	Asymptotic normal
Method	Normal approximation
Number of Sides	2
Alpha	0.05
Nominal Power	0.9
Null Relative Risk	1

Computed N per Group				
Index	Ref Proportion	Relative Risk	Actual Power	N per Group
1	0.23	0.4	0.900	147
2	0.23	0.5	0.900	225
3	0.23	0.6	0.900	371
4	0.23	0.7	0.900	693
5	0.23	0.8	0.900	1629
6	0.26	0.4	0.901	127
7	0.26	0.5	0.901	194
8	0.26	0.6	0.900	318
9	0.26	0.7	0.900	593
10	0.26	0.8	0.900	1391
11	0.29	0.4	0.902	111
12	0.29	0.5	0.902	169
13	0.29	0.6	0.901	277
14	0.29	0.7	0.900	514
15	0.29	0.8	0.900	1203