

Appendix 2: definition of serious adverse event

The following definition of serious adverse event (SAE) was used, according to the Article 2 of Clinical Trials Regulation (EU) No 536/2014: “Any untoward medical occurrence or effect that at any dose requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening or results in death”, considered at the time of the event.

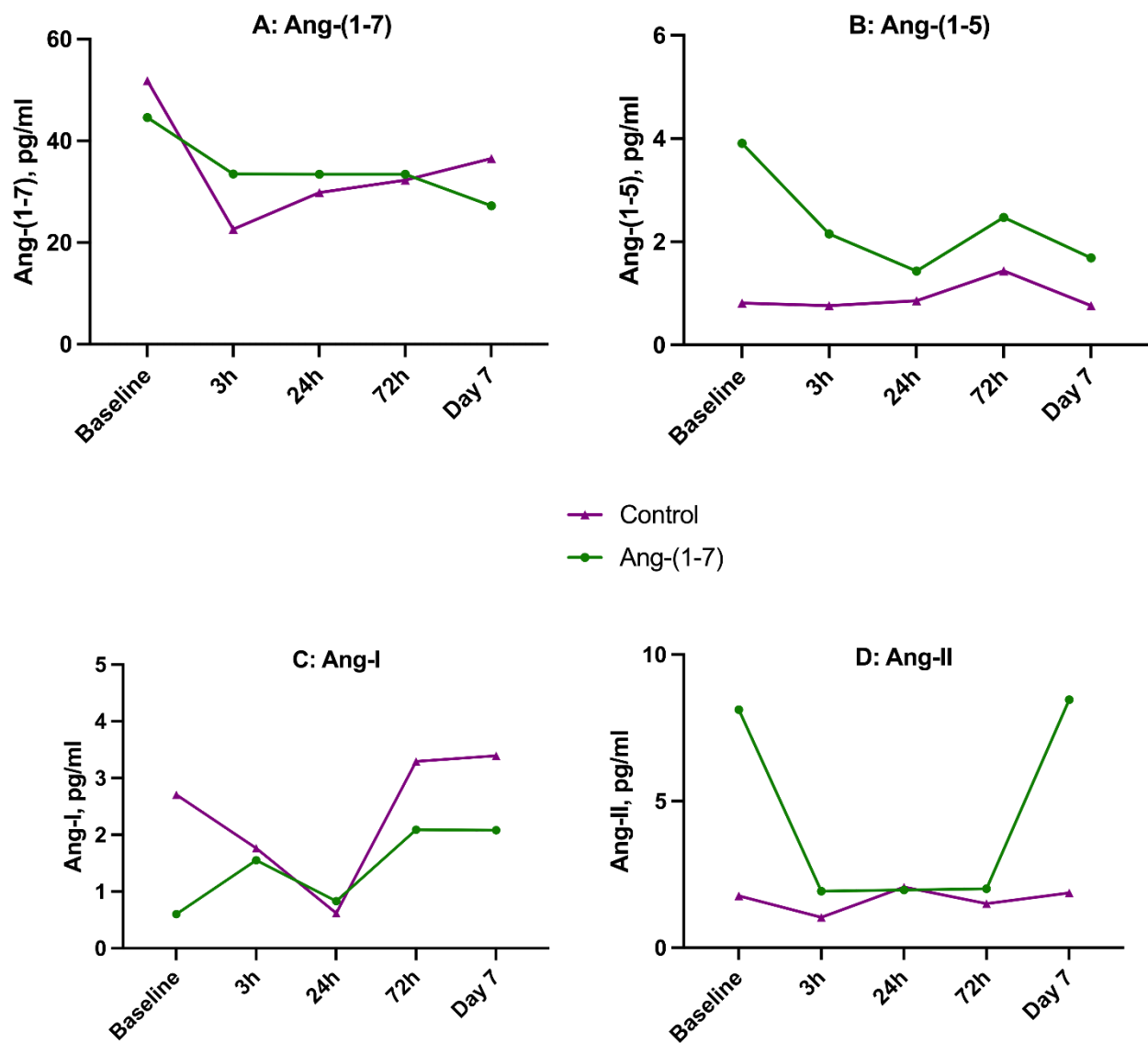
SAEs should include all serious events independent of whether they have a suspected causal relationship to the investigational medicinal product or not.

Supplementary Table 1: Subgroup analysis for oxygen free days by day 28.

Subgroup (n/n)		Ang-(1-7)	Controls	<i>p</i>
		Phase 2		
Age	< 60 years old (24/23)	19.5 [3.5-21]	14 [0-18]	0.07
	≥ 60 years old (8/22)	9.5 [0-20.5]	13.5 [0-18.25]	0.97
Sex at birth	Male (21/24)	19 [1-21]	5 [0-16]	0.09
	Female (11/18)	19 [0-20]	15 [5.25-19.25]	0.83
Obesity (BMI > 30 Kg/m)	Yes (16-15)	15 [0-20]	14 [0-16]	0.48
	No (18/28)	19 [6.5-21.25]	13 [0-19.75]	0.11
ACEi/ARBs	Yes (7/10)	11 [0-21]	12.5 [2.25-20.25]	0.78
	No (21/29)	19 [5-21]	14 [0-16.5]	0.051
		Pooled Phase 1+2		
Age	< 60 years old (41/23)	20 [9.5-21.5]	14 [0-18]	0.009
	≥ 60 years old (19/22)	0 [0-19]	13.5 [0-18.25]	0.52
Sex at birth	Male (26/24)	19 [6.5-21]	5 [0-16]	0.03
	Female (33/18)	14 [0-22]	15 [5.25-19.25]	0.65
Obesity (BMI > 30 Kg/m)	Yes (26/15)	19 [7.5-21]	14 [0-16]	0.06
	No (33/28)	19 [1-22]	13 [0-19.75]	0.19
ACEi/ARBs	Yes (17/10)	19 [6-22.5]	12.5 [2.25-20.25]	0.33
	No (38/29)	19 [0-21]	14 [0-16.5]	0.09

BMI= body mass index; ACEi= angiotensin converting enzyme inhibitors, ARBs= angiotensin receptor blockers.

Supplementary Figure 1: Circulating RAS peptides. A: Ang-(1-7); B: Ang-(1-5); C: Ang-I; D: Ang-II. Points represent median values.



Supplementary Figure 2: time evolution of creatinine (A), C-reactive protein (CRP, B), daily fluid balance (C) and temperature (D). Points represents median values and bars interquartile ranges.

