SUPPLEMENTARY FILES

High-Dose Intravenous Vitamin C Treatment- a 10-Year Prospective Cohort Study (HIVITC)

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Supplementary Table 1: Eligibility criteria for the HIVITC study according to the safety-related chapters of the official German Summary of Product Characteristics (SmPC) for Pascorbin® 7.5 g. In the standard procedure for observational studies, the relevant chapters of the SmPC are the guidelines for physicians and natural health practitioners for the treatment decisions in general, and to include or exclude patients in the study.

Inclusion criteria
Age of ≥ 12 years
Treatment with vitamin C infusion (7.5 g) due to vitamin C deficiency
Patient's statement of agreement to use and publish their data for the observational study
Exclusion criteria
Oxalate urolithiasis
Iron storage disease (thalassemia, hemochromatosis, sideroblastic anemia)
Patients that recently received RBC units transfused
Age of < 12 years
Pregnancy and lactation
Hypersensitivity to an ingredient
Children
Age of < 12: parental administration of 5-7 mg ascorbic acid/kg bodyweight (bw) per day should not be exceeded
Treatment of methemoglobinemia in children: a daily dose of 100 mg ascorbic acid/kg bw should not be exceeded
Precautions/ warnings
Intravenous injection of high doses of Pascorbin® can lead to acute renal failure due to precipitation of calcium oxalate crystals in the kidneys as a result of kidney stones
Renal insufficiency
Patients with recurrent kidney stone formation
Severe or terminal renal insufficiency (dialysis patients)
Patients who follow a low-salt diet
Erythrocytic glucose-6-phosphate dehydrogenase deficiency (G6PD)
Patients with known obstructive and restrictive bronchial and pulmonary diseases may experience acute dyspnoea
Patients living with diabetes and regular glucose monitoring: parenteral administration of high-dose IVC may interfere with the detection reaction of blood glucose by rapid glucose tests

Supplementary Table 2: Sum score changes non-specific symptoms (0 - 12 points).

Patient group	n (Start/End/ Difference)	Mean sum score (SD), [95 % CI]		Difference (SD), [95 % CI]	P value*
		Start of observation	End of observation		
Total population	5109/5102/5101	5.1 (3.26) [4.97 to 5.15	1.0 (1.73) [0.98 to 1.07]	-4.0 (2.96) [-4.12 to -3.96]	<0.0001
With MUD	2698/2698/2698	4.2 (2.92) [4.13 to 4.35]	0.7 (1.50) [0.68 to 0.79]	-3.5 (2.61) [-3.60 to -3.41]	<0.0001
Without MUD	2408/2401/2400	6.0 (3.37) [5.84 to 6.11]	1.3 (1.90) [1.27 to 1.42]	-4.6 (3.21) [-4.77 to -4.51]	<0.0001
Therapy duration < 2 weeks	2525/2525/2525	4.1 (3.05) [4.03 to 4.27]	0.3 (1.08) [0.29 to 0.38]	-3.8 (2.89) [-3.93 to -3.70]	<0.0001
Therapy duration 2 - 4 weeks	706/705/705	5.2 (3.27) [4.94 to 5.42]	1.4 (1.91) [1.30 to 1.58]	-3.7 (3.18) [-3.98 to -3.51]	<0.0001
Therapy duration ≥ 4 weeks	1876/1870/1869	6.2 (3.13) [6.10 to 6.38]	1.8 (1.97) [1.71 to 1.89]	-4.4 (2.91) [-4.58 to -4.31]	<0.0001

*one sample t-test, the difference "post minus pre" was calculated for total population (n = 5101), patients with medication of underlying disease (MUD) (n = 2698), patients without MUD (n = 2400), patients with a therapy duration of < 2 weeks (n = 2525), patients with a therapy duration of 2 - 4 weeks (n = 705) and for patients with a therapy duration of > 4 weeks (n = 1869). Groups with different therapy duration include patients with- and without MUD. Difference in change between MUD and without MUD groups: $p < 0.0001$, Kruskal-Wallis-test. Difference in change between therapy duration groups: $p < 0.0001$, Kruskal-Wallis-test.

Supplementary Table 3: Sum score changes pain (0 - 10 points).

Patient group	n (Start/End/ Difference)	Mean sum score (SD), [95 % CI]		Difference (SD), [95 % CI]	P value*
		Start of observation	End of observation		
Total population	3928/3933/3928	4.7 (2.94) [4.65 to 4.83]	1.1 (1.77) [1.01 to 1.12]	-3.7 (2.73) [-3.76 to -3.59]	<0.0001
With MUD	1983/1983/1983	3.7 (2.58) [3.58 to 3.81]	0.7 (1.48) [0.59 to 0.72]	-3.0 (2.28) [-3.14 to -2.94]	<0.0001
Without MUD	1943/1948/1943	5.8 (2.90) [5.68 to 5.94]	1.5 (1.94) [1.39 to 1.56]	-4.3 (2.98) [-4.46 to -4.20]	<0.0001
Therapy duration < 2 weeks	1911/1911/1911	4.0 (2.86) [3.86 to 4.11]	0.2 (0.94) [0.20 to 0.28]	-3.7 (2.78) [-3.87 to -3.62]	<0.0001
Therapy duration 2 - 4 weeks	480/480/480	5.0 (3.02) [4.76 to 5.31]	1.4 (1.87) [1.21 to 1.54]	-3.7 (3.08) [-3.93 to -3.38]	<0.0001
Therapy duration ≥ 4 weeks	1535/1540/1535	5.6 (2.76) [5.44 to 5.72]	2.0 (2.02) [1.88 to 2.08]	-3.6 (2.53) [-3.72 to -3.47]	<0.0001

*one sample t-test, the difference "post minus pre" was calculated for total population (n = 3928), patients with medication of underlying disease (MUD) (n = 1983), patients without MUD (n = 1943), patients with a therapy duration of < 2 weeks (n = 1911), patients with a therapy duration of 2 - 4 weeks (n = 480) and for patients with a therapy duration of > 4 weeks (n = 1535). Groups with different therapy duration include patients with- and without MUD. Difference in change between MUD and without MUD groups: $p < 0.0001$, Kruskal-Wallis-test. Difference in change between therapy duration groups: $p = 0.3936$, Kruskal-Wallis-test.

Supplementary Table 4: Sum score changes disease-specific symptoms (0 - 9 points).

Patient group	n (Start/End/ Difference)	Mean sum score (SD), [95 % CI]		Difference (SD), [95 % CI]	P value*
		Start of observation	End of observation		
Total population	5246/5248/5246	4.9 (2.26) [4.87 to 4.99]	0.9 (1.37) [0.84 to 0.91]	-4.1 (2.27) [-4.12 to -3.99]	<0.0001
With MUD	2858/2858/2858	4.7 (1.96) [4.62 to 4.76]	0.7 (1.29) [0.65 to 0.74]	-4.0 (1.99) [-4.07 to -3.92]	<0.0001
Without MUD	2385/2387/2385	5.2 (2.55) [5.12 to 5.32]	1.1 (1.43) [1.04 to 1.15]	-4.1 (2.56) [-4.23 to -4.02]	<0.0001
Therapy duration < 2 weeks	2623/2623/2623	4.6 (2.25) [4.48 to 4.65]	0.3 (0.79) [0.25 to 0.31]	-4.3 (2.22) [-4.37 to -4.20]	<0.0001
Therapy duration 2 - 4 weeks	765/765/765	5.0 (2.14) [4.88 to 5.18]	1.4 (1.61) [1.28 to 1.51]	-3.6 (2.32) [-3.80 to -3.47]	<0.0001
Therapy duration ≥ 4 weeks	1856/1858/1856	5.4 (2.22) [5.31 to 5.51]	1.5 (1.53) [1.43 to 1.57]	-3.9 (2.29) [-4.01 to -3.80]	<0.0001

*one sample t-test, the difference "post minus pre" was calculated for total population (n = 5246), patients with medication of underlying disease (MUD) (n = 2858), patients without MUD (n = 2385), patients with a therapy duration of < 2 weeks (n = 2623), patients with a therapy duration of 2 - 4 weeks (n = 765) and for patients with a therapy duration of > 4 weeks (n = 1856). Groups with different therapy duration include patients with- and without MUD. Difference in change between MUD and without MUD groups: $p = 0.6711$, Kruskal-Wallis-test. Difference in change between therapy duration groups: $p < 0.0001$, Kruskal-Wallis-test.

Supplementary Table 5: All documented disease-specific symptoms categorized according to respective system organ class (SOC).

Disease-specific symptoms (SOC)**	**N**	**%**
infections and infestations	272	2.20 %
blood and lymphatic system disorders	54	0.40 %
immune system disorders	67	0.50 %
metabolism and nutrition disorders	95	0.80 %
psychiatric disorders	752	6.10 %
nervous system disorders	1266	10.30 %
eye disorders	183	1.50 %
ear and labyrinth disorders	314	2.60 %
cardiac disorders	71	0.60 %
vascular disorders	138	1.10 %
respiratory thoracic and mediastinal disorders	3061	24.90 %
gastrointestinal disorder	1251	10.20 %
skin and subcutaneous tissue disorders	831	6.80 %
musculoskeletal and connective tissue disorders	1150	9.30 %
renal and urinary disorders	977	7.90 %
reproductive system and breast disorders	48	0.40 %
general disorders and administration site conditions	1661	13.50 %
investigations	20	0.20 %
hepatobiliary disorders	5	0.00 %
injury, poisoning and procedural complications	81	0.70 %
social circumstances	4	0.00 %
endocrine disorders	3	0.00 %
neoplasms benign, malignant and unspecified (incl. cysts and polyps)	2	0.00 %
social circumstances	1	0.00 %
Valid data	12307	100
Missing data	3	0

** Based on an entity of 12310 disease-specific symptoms

Supplementary Table 6: Ranking of the ICD-10 groups of the underlying diseases according to frequency of mention.

ICD-10 group	**n**	**%**
J00 - J99: Diseases of the respiratory system	1951	34.7
A00 - B99: Certain infectious and parasitic diseases	989	17.6
F00 - F99: Emotional and behavioral disorders	360	6.4
Z00 - Z99: Factors that influence the state of health and make demands on the public health system	342	6.1
M00 - M99: Diseases of the musculoskeletal system and connective tissue	331	5.9
C00 - D48: Neoplasms	329	5.8
N00 - N99: Diseases of the genitourinary system	325	5.8
L00 - L99: Diseases of the skin and subcutis	217	3.9
K00 - K93: Diseases of the digestive system	202	3.6
R00 - R99: Symptoms and abnormal clinical and lab findings that are not classified elsewhere	140	2.5
G00 - G99: Diseases of the nervous system	100	1.8
S00 - T98: Injury, poisoning and certain other external causes	99	1.8
H60 - H95: Diseases of the ear and mastoid process	65	1.2
I00 - I99: Diseases of the circulatory system	47	0.8
D50 - D90: Diseases of the blood and blood-forming organs and certain disorders involving the immune system	44	0.8
E00 - E90: Endocrine, nutritional and metabolic diseases	34	0.6
U00 - U99: Key numbers for special purposes	27	0.5
H00 - H59: Diseases of the eye and adnexa	7	0.1
Q00 - Q99: Congenital malformations, deformities and chromosomal anomalies	2	0.0
V01 - Y84: External causes of morbidity and mortality	1	0.0
Not applicable to ICD-10 or not clear	*16*	*0.3*
Valid data	**5628**	**100**