

Table S1 Patients' medical history

Variables	Total (n=225), persons (%) [case]	Placebo (n=55), persons (%) [case]	Synatura syrup (n=49), persons (%) [case]	CKD-497 200 mg (n=68), persons (%) [case]	CKD-497 300 mg (n=53), persons (%) [case]	P value
Total	53 (23.56) [99]	13 (23.64) [24]	11 (22.45) [26]	14 (20.59) [28]	15 (28.30) [21]	0.7942 ^b
Gastrointestinal disorders	11 (4.89) [13]	2 (3.64) [2]	3 (6.12) [3]	4 (5.88) [6]	2 (3.77) [2]	0.8840 ^a
Gastroesophageal reflux disease	4 (1.78) [4]	1 (1.82) [1]	0 (0.00) [0]	2 (2.94) [2]	1 (1.89) [1]	0.9066 ^a
Chronic gastritis	2 (0.89) [2]	1 (1.82) [1]	0 (0.00) [0]	1 (1.47) [1]	0 (0.00) [0]	1.0000 ^a
Gastritis	2 (0.89) [2]	0 (0.00) [0]	1 (2.04) [1]	0 (0.00) [0]	1 (1.89) [1]	0.3537 ^a
Colitis	1 (0.44) [1]	0 (0.00) [0]	1 (2.04) [1]	0 (0.00) [0]	0 (0.00) [0]	0.2178 ^a
Colitis ulcerative	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.47) [1]	0 (0.00) [0]	1.0000 ^a
Duodenitis	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.47) [1]	0 (0.00) [0]	1.0000 ^a
Gingival bleeding	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.47) [1]	0 (0.00) [0]	1.0000 ^a
Irritable bowel syndrome	1 (0.44) [1]	0 (0.00) [0]	1 (2.04) [1]	0 (0.00) [0]	0 (0.00) [0]	0.2178 ^a
Vascular disorders	10 (4.44) [10]	3 (5.45) [3]	2 (4.08) [2]	4 (5.88) [4]	1 (1.89) [1]	0.7728 ^a
Hypertension	7 (3.11) [7]	2 (3.64) [2]	1 (2.04) [1]	3 (4.41) [3]	1 (1.89) [1]	0.8782 ^a
Varicose vein	2 (0.89) [2]	1 (1.82) [1]	0 (0.00) [0]	1 (1.47) [1]	0 (0.00) [0]	1.0000 ^a
Peripheral venous disease	1 (0.44) [1]	0 (0.00) [0]	1 (2.04) [1]	0 (0.00) [0]	0 (0.00) [0]	0.2178 ^a
Musculoskeletal and connective tissue disorders	9 (4.00) [12]	3 (5.45) [5]	4 (8.16) [5]	1 (1.47) [1]	1 (1.89) [1]	0.2503 ^a
Back pain	2 (0.89) [2]	1 (1.82) [1]	1 (2.04) [1]	0 (0.00) [0]	0 (0.00) [0]	0.4607 ^a
Osteoarthritis	2 (0.89) [2]	0 (0.00) [0]	1 (2.04) [1]	1 (1.47) [1]	0 (0.00) [0]	0.7086 ^a
Rotator cuff syndrome	2 (0.89) [2]	1 (1.82) [1]	1 (2.04) [1]	0 (0.00) [0]	0 (0.00) [0]	0.4607 ^a
Arthralgia	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (1.89) [1]	0.4533 ^a
Facet joint syndrome	1 (0.44) [1]	1 (1.82) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	0.6978 ^a
Myofascial pain syndrome	1 (0.44) [1]	0 (0.00) [0]	1 (2.04) [1]	0 (0.00) [0]	0 (0.00) [0]	0.2178 ^a
Pain in extremity	1 (0.44) [1]	0 (0.00) [0]	1 (2.04) [1]	0 (0.00) [0]	0 (0.00) [0]	0.2178 ^a
Patellofemoral pain syndrome	1 (0.44) [1]	1 (1.82) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	0.6978 ^a
Soft tissue disorder	1 (0.44) [1]	1 (1.82) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	0.6978 ^a
Endocrine disorders	8 (3.56) [9]	3 (5.45) [3]	2 (4.08) [2]	0 (0.00) [0]	3 (5.66) [4]	0.1700 ^a
Hypothyroidism	6 (2.67) [6]	2 (3.64) [2]	2 (4.08) [2]	0 (0.00) [0]	2 (3.77) [2]	0.3380 ^a
Autoimmune thyroiditis	2 (0.89) [2]	1 (1.82) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.89) [1]	0.5763 ^a
Goiter	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (1.89) [1]	0.4533 ^a
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (3.11) [7]	2 (3.64) [2]	1 (2.04) [1]	2 (2.94) [2]	2 (3.77) [2]	1.0000 ^a
Benign neoplasm of thyroid gland	2 (0.89) [2]	1 (1.82) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.89) [1]	0.5763 ^a
Benign ovarian tumor	2 (0.89) [2]	1 (1.82) [1]	1 (2.04) [1]	0 (0.00) [0]	0 (0.00) [0]	0.4607 ^a
Benign hepatic neoplasm	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.47) [1]	0 (0.00) [0]	1.0000 ^a
Fibroadenoma of breast	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.47) [1]	0 (0.00) [0]	1.0000 ^a
Large intestine benign neoplasm	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (1.89) [1]	0.4533 ^a
Metabolism and nutrition disorders	6 (2.67) [8]	1 (1.82) [1]	0 (0.00) [0]	3 (4.41) [5]	2 (3.77) [2]	0.5674 ^a
Diabetes mellitus	3 (1.33) [3]	1 (1.82) [1]	0 (0.00) [0]	1 (1.47) [1]	1 (1.89) [1]	1.0000 ^a
Glucose tolerance impaired	2 (0.89) [2]	0 (0.00) [0]	0 (0.00) [0]	1 (1.47) [1]	1 (1.89) [1]	0.8516 ^a
Hyperlipidemia	2 (0.89) [2]	0 (0.00) [0]	0 (0.00) [0]	2 (2.94) [2]	0 (0.00) [0]	0.2507 ^a
Hypercholesterolemia	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.47) [1]	0 (0.00) [0]	1.0000 ^a
Respiratory, thoracic and mediastinal disorders	6 (2.67) [6]	2 (3.64) [2]	3 (6.12) [3]	1 (1.47) [1]	0 (0.00) [0]	0.2195 ^a
Rhinitis allergic	3 (1.33) [3]	1 (1.82) [1]	1 (2.04) [1]	1 (1.47) [1]	0 (0.00) [0]	0.8942 ^a
Cough	1 (0.44) [1]	1 (1.82) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	0.6978 ^a
Oropharyngeal pain	1 (0.44) [1]	0 (0.00) [0]	1 (2.04) [1]	0 (0.00) [0]	0 (0.00) [0]	0.2178 ^a
Restrictive pulmonary disease	1 (0.44) [1]	0 (0.00) [0]	1 (2.04) [1]	0 (0.00) [0]	0 (0.00) [0]	0.2178 ^a
Infections and infestations	5 (2.22) [5]	0 (0.00) [0]	2 (4.08) [2]	2 (2.94) [2]	1 (1.89) [1]	0.5564 ^a
Periodontitis	2 (0.89) [2]	0 (0.00) [0]	1 (2.04) [1]	0 (0.00) [0]	1 (1.89) [1]	0.3537 ^a
Gastroenteritis	1 (0.44) [1]	0 (0.00) [0]	1 (2.04) [1]	0 (0.00) [0]	0 (0.00) [0]	0.2178 ^a
Gingivitis	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.47) [1]	0 (0.00) [0]	1.0000 ^a
Pyelonephritis chronic	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.47) [1]	0 (0.00) [0]	1.0000 ^a
Skin and subcutaneous tissue disorders	5 (2.22) [5]	1 (1.82) [1]	3 (6.12) [3]	0 (0.00) [0]	1 (1.89) [1]	0.1356 ^a
Androgenetic alopecia	2 (0.89) [2]	1 (1.82) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.89) [1]	0.5763 ^a
Chloasma	1 (0.44) [1]	0 (0.00) [0]	1 (2.04) [1]	0 (0.00) [0]	0 (0.00) [0]	0.2178 ^a
Lentigo	1 (0.44) [1]	0 (0.00) [0]	1 (2.04) [1]	0 (0.00) [0]	0 (0.00) [0]	0.2178 ^a
Mechanical urticaria	1 (0.44) [1]	0 (0.00) [0]	1 (2.04) [1]	0 (0.00) [0]	0 (0.00) [0]	0.2178 ^a
Investigations	4 (1.78) [5]	2 (3.64) [2]	0 (0.00) [0]	1 (1.47) [2]	1 (1.89) [1]	0.7267 ^a
Alanine aminotransferase increased	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (1.89) [1]	0.4533 ^a
Blood lactate dehydrogenase increased	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.47) [1]	0 (0.00) [0]	1.0000 ^a
Blood pressure increased	1 (0.44) [1]	1 (1.82) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	0.6978 ^a
Transaminases increased	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.47) [1]	0 (0.00) [0]	1.0000 ^a
Ultrasound breast abnormal	1 (0.44) [1]	1 (1.82) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	0.6978 ^a
Eye disorders	4 (1.78) [4]	0 (0.00) [0]	2 (4.08) [2]	0 (0.00) [0]	2 (3.77) [2]	0.1272 ^a
Dry eye	2 (0.89) [2]	0 (0.00) [0]	1 (2.04) [1]	0 (0.00) [0]	1 (1.89) [1]	0.3537 ^a
Ulcerative keratitis	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (1.89) [1]	0.4533 ^a
Vitreous detachment	1 (0.44) [1]	0 (0.00) [0]	1 (2.04) [1]	0 (0.00) [0]	0 (0.00) [0]	0.2178 ^a
Reproductive system and breast disorders	4 (1.78) [4]	1 (1.82) [1]	2 (4.08) [2]	1 (1.47) [1]	0 (0.00) [0]	0.5339 ^a
Benign prostatic hyperplasia	1 (0.44) [1]	0 (0.00) [0]	1 (2.04) [1]	0 (0.00) [0]	0 (0.00) [0]	0.2178 ^a
Breast mass	1 (0.44) [1]	0 (0.00) [0]	1 (2.04) [1]	0 (0.00) [0]	0 (0.00) [0]	0.2178 ^a
Fibrocystic breast disease	1 (0.44) [1]	1 (1.82) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	0.6978 ^a
Infertility male	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.47) [1]	0 (0.00) [0]	1.0000 ^a
Congenital, familial and genetic disorders	2 (0.89) [2]	0 (0.00) [0]	0 (0.00) [0]	1 (1.47) [1]	1 (1.89) [1]	0.8516 ^a
Type IIa hyperlipidemia	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.47) [1]	0 (0.00) [0]	1.0000 ^a
Type V hyperlipidemia	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (1.89) [1]	0.4533 ^a
Hepatobiliary disorders	2 (0.89) [2]	1 (1.82) [1]	0 (0.00) [0]	1 (1.47) [1]	0 (0.00) [0]	1.0000 ^a
Hepatic calcification	1 (0.44) [1]	1 (1.82) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	0.6978 ^a
Liver disorder	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.47) [1]	0 (0.00) [0]	1.0000 ^a
Nervous system disorders	2 (0.89) [2]	1 (1.82) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.89) [1]	0.5763 ^a
Diabetic neuropathy	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (1.89) [1]	0.4533 ^a
Piriformis syndrome	1 (0.44) [1]	1 (1.82) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	0.6978 ^a
Blood and lymphatic system disorders	1 (0.44) [1]	0 (0.00) [0]	1 (2.04) [1]	0 (0.00) [0]	0 (0.00) [0]	0.2178 ^a
Iron deficiency anemia	1 (0.44) [1]	0 (0.00) [0]	1 (2.04) [1]	0 (0.00) [0]	0 (0.00) [0]	0.2178 ^a
Cardiac disorders	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.47) [1]	0 (0.00) [0]	1.0000 ^a
Ventricular extrasystoles	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.47) [1]	0 (0.00) [0]	1.0000 ^a
Immune system disorders	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (1.89) [1]	0.4533 ^a
Food allergy	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (1.89) [1]	0.4533 ^a
Renal and urinary disorders	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (1.89) [1]	0.4533 ^a
Hematuria	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (1.89) [1]	0.4533 ^a
Surgical and medical procedures	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.47) [1]	0 (0.00) [0]	1.0000 ^a
Dental implantation	1 (0.44) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (1.47) [1]	0 (0.00) [0]	1.0000 ^a

^a, Kruskal-Wallis test; ^b, Fisher's exact test.

Table S2 Drug compliance

Variables	Total (n=225)	Placebo (n=55)	Synatura (n=49)	CKD-497 200 mg (n=68)	CKD-497 300 mg (n=53)	P value
Total drug compliance, mean \pm SD	98.60 \pm 4.76	99.35 \pm 3.24	98.04 \pm 5.83	98.97 \pm 4.15	97.87 \pm 5.60	0.6346 ^a
Assessment of total drug compliance, n (%)						
\leq 80% or \geq 120%	223 (99.11)	55 (100.0)	48 (97.96)	68 (100.0)	52 (98.11)	0.3537 ^b
>80% or <120%	2 (0.89)	0 (0.00)	1 (2.04)	0 (0.00)	1 (1.89)	

^a, Kruskal-Wallis test; ^b, Fisher's exact test. SD, standard deviation.

Table S3 Secondary efficacy analysis of BSS (cough and phlegm)

Variables	Placebo (n=55)	Synatura (n=49)	CKD-497 200 mg (n=68)	CKD-497 300 mg (n=53)
Cough				
Baseline (visit 1), mean (SD)	2.47 (0.54)	2.45 (0.54)	2.54 (0.56)	2.58 (0.53)
Day 4 (visit 2), mean (SD)	1.56 (0.76)	1.35 (0.66)	1.40 (0.79)	1.45 (0.72)
Day 7 (visit 3), mean (SD)	0.80 (0.85)	0.63 (0.76)	0.81 (0.82)	0.68 (0.78)
P value ¹			0.3411	
P value ²			0.6346	
Phlegm				
Baseline (visit 1), mean (SD)	2.40 (0.53)	2.35 (0.48)	2.25 (0.44)	2.25 (0.43)
Day 4 (visit 2), mean (SD)	1.56 (0.90)	1.35 (0.72)	1.43 (0.65)	1.13 (0.71)
Day 7 (visit 3), mean (SD)	0.84 (0.88)	0.69 (0.71)	0.75 (0.78)	0.57 (0.67)
P value ¹			0.1363	
P value ²			0.6404	

¹, result of Kruskal-Wallis test comparing group's average of changes between day 4 (visit 2) and baseline (visit 1); ², result of Kruskal-Wallis test comparing group's average of changes between day 7 (visit 3) and baseline (visit 1). BSS, bronchitis severity score; SD, standard deviation.

Table S4 Analysis of covariance with an adjustment for a baseline value

Variables (BSS total)	Placebo (n=55)	Synatura (n=49)	CKD-497 200 mg (n=68)	CKD-497 300 mg (n=53)
Baseline (visit 1), mean (SD)	5.82 (1.20)	5.63 (0.88)	5.68 (0.98)	5.72 (0.91)
Day 4 (visit 2), mean (SD)	3.56 (2.32)	2.88 (1.36)	3.10 (1.53)	2.85 (1.59)
Day 7 (visit 3), mean (SD)	1.78 (2.02)	1.33 (1.28)	1.59 (1.37)	1.43 (1.77)
P value ¹			0.1488	
P value ²			0.6169	

¹, result of ANCOVA test comparing group's average of changes between day 4 (visit 2) and baseline (visit 1); ², result of ANCOVA test comparing group's average of changes between day 7 (visit 3) and baseline (visit 1). BSS, bronchitis severity score; SD, standard deviation.

Table S5 Secondary effectiveness analysis of BSS (cough baseline score ≥ 3)

Variables (cough)	Placebo (n=25)	Synatura (n=21)	CKD-497 200 mg (n=35)	CKD-497 300 mg (n=30)
Baseline (visit 1), mean (SD)	6.20 (1.44)	5.76 (0.89)	5.86 (1.17)	5.97 (0.96)
Day 4 (visit 2), mean (SD)	4.00 (3.06)	3.10 (1.58)	3.37 (1.72)	3.30 (1.86)
Day 7 (visit 3), mean (SD)	2.20 (2.65)	1.57 (1.50)	1.94 (1.53)	1.87 (2.16)
P value ¹			0.9144	
P value ²			0.7948	

¹, result of Kruskal-Wallis test comparing group's average of changes between day 4 (visit 2) and baseline (visit 1); ², result of Kruskal-Wallis test comparing group's average of changes between day 7 (visit 3) and baseline (visit 1). BSS, bronchitis severity score; SD, standard deviation.

Table S6 Secondary effectiveness analysis of BSS (phlegm baseline score ≥ 3)

Variables (phlegm)	Placebo (n=21)	Synatura (n=17)	CKD-497 200 mg (n=17)	CKD-497 300 mg (n=13)
Baseline (visit 1), mean (SD)	6.24 (1.55)	5.88 (0.93)	6.29 (1.40)	6.46 (1.13)
Day 4 (visit 2), mean (SD)	5.00 (2.95)	3.35 (1.77)	3.59 (1.87)	3.77 (2.55)
Day 7 (visit 3), mean (SD)	2.76 (2.81)	1.53 (1.46)	1.76 (1.52)	2.15 (3.08)
P value ¹			0.0421	
P value ²			0.5598	

¹, result of Kruskal-Wallis test comparing group's average of changes between day 4 (visit 2) and baseline (visit 1); ², result of Kruskal-Wallis test comparing group's average of changes between day 7 (visit 3) and baseline (visit 1). BSS, bronchitis severity score; SD, standard deviation.