

Supplementary Material 7: Safety Analysis

Adverse Events	Number of Studies	Sample Size	Risk Ratio (95% Confidence Interval)	I ²	Cochran Q	p-value
<i>General Disorders</i>						
TEAE/adverse events	10	21684	1.06 (1.00 to 1.13)	79.80%	< 0.01	0.04*
Serious TEAE/adverse events	15	65123	0.86 (0.55 to 1.34)	83.70%	< 0.01	0.48
Severe TEAE/adverse events	3	13056	0.98 (0.97 to 1.00)	0.00%	0.98	0.04*
Death	2	1320	0.18 (0.06 to 0.59)	0.00%	0.93	0.03
Any benign neoplasm	3	12945	0.98 (0.17 to 5.65)	49.50%	0.14	0.97
Any Cancer/Malignant neoplasm	7	52524	1.00 (0.96 to 1.05)	0.00%	0.96	0.87
Premalignant neoplasm	1	3297	2.00 (0.69 to 5.84)	-	-	0.20
Neoplasms benign, malignant, and unspecified	4	17582	1.02 (0.90 to 1.14)	0.00%	0.59	0.71
Infections and Infestations	4	29028	0.98 (0.92 to 1.04)	12.80%	0.33	0.32

Fatigue	2	2565	1.35 (0.47 to 3.90)	0.00%	0.57	0.17
Solomnence	1	308	1.51 (0.06 to 36.77)	-	-	-
Weight decreased	1	317	7.24 (0.43 to 122.12)	-	-	-
Volume depletion related AEs	1	464	0.50 (0.09 to 2.73)	-	-	0.43
Peripheral edema	1	2248	0.56 (0.38 to 0.82)	-	-	<0.01*

Gastrointestinal

Gastrointestinal disorders	8	28417	1.55 (1.22 to 1.97)	84.10%	<0.01	<0.01*
Nausea	12	14115	3.56 (2.43 to 5.21)	79.90%	<0.01	<0.01*
Vomiting	9	12924	3.99 (2.44 to 6.54)	80.50%	<0.01	<0.01*
Diarrhea	12	14148	1.85 (1.33 to 2.59)	52.80%	0.02	<0.01*
Constipation	4	3234	2.04 (1.46 to 2.83)	0.00%	0.42	<0.01*
Appendicitis	1	9432	0.37 (0.10 to 1.41)	-	-	0.15
Abdominal pain	2	2565	1.54 (0.21 to 11.42)	0.00%	0.78	0.22
Dyspepsia	2	2565	3.12 (0.00 to 29469.19)	37.20%	0.21	0.36
Eructation	2	2565	10.14 (2.23 to 46.11)	0.00%	0.80	0.03

Flatulence	1	3002	4.05 (2.50 to 6.57)	-	-	<0.01*
Gastroesophageal reflux disease	2	2565	2.75 (0.94 to 8.03)	0.00%	0.73	0.05
Gastroenteritis	1	2248	1.54 (1.11 to 2.12)			0.01*
<i>Neurological</i>						
Nervous System Disorders	3	14285	1.04 (1.00 to 1.09)	0.00%	0.89	0.05
Headache	6	4146	1.10 (0.91 to 1.32)	0.00%	0.65	0.26
Dizziness	4	3263	1.39 (1.03 to 1.87)	0.00%	0.71	0.04*
Hyperaesthesia	1	308	1.51 (0.06 to 36.77)	-	-	
Loss of Consciousness	1	206	3.00 (0.12 to 72.79)	-	-	
Parkinson's Disease	1	308	1.51 (0.06 to 36.77)	-	-	
Dementia	1	308	1.51 (0.06 to 36.77)	-	-	
Diabetic Neuropathy	2	15040	1.03 (0.82 to 1.30)	0.00%	0.81	0.33
<i>Psychiatry</i>						
Psychiatric Disorders	1	4076	1.18 (0.79 to 1.77)	-	-	0.41
<i>Dermatology</i>						

Skin and Subcutaneous Tissue Disorders	2	13977	0.90 (0.58 to 1.42)	0.00%	0.44	0.21
Injection-site reactions	5	8673	1.52 (0.60 to 3.87)	51.90%	0.08	0.28
Injection site hematoma	1	2248	0.75 (0.55 to 1.03)	-	-	0.08
<i>Cardiology</i>						
Cardiac disorders	5	18128	0.98 (0.90 to 1.06)	2.00%	0.40	0.52
Atrial fibrillation	1	3297	0.86 (0.59 to 1.25)	-	-	0.44
Atrial fibrillation or flutter	2	24169	0.90 (0.47 to 1.71)	0.00%	0.44	0.28
<i>Pulmonary</i>						
Pneumonia	1	9432	0.95 (0.75 to 1.20)	-	-	0.66
Bronchitis	1	2248	0.92 (0.68 to 1.23)	-	-	0.56
Cough	1	2248	0.94 (0.69 to 1.27)	-	-	0.67
Oropharyngeal pain	1	2248	0.84 (0.58 to 1.20)	-	-	0.34
Respiratory, Thoracic and Mediastinal Disorders	2	13977	0.93 (0.20 to 4.40)	75.60%	0.04	0.67

Upper Respiratory Tract Infection	4	3481	0.91 (0.70 to 1.19)	0.00%	0.47	0.35
<i>Renal</i>						
Renal and Urinary Disorders	2	13977	0.89 (0.61 to 1.30)	0.00%	0.40	0.16
Acute Renal Injury	2	3647	0.85 (0.15 to 4.75)	0.00%	0.57	0.44
Acute Renal Failure	5	29585	1.02 (0.74 to 1.40)	39.10%	0.16	0.88
Urinary Tract Infection	2	2712	1.35 (0.51 to 3.56)	0.00%	0.62	0.16
<i>Hepatobiliary</i>						
Overall pancreatitis	5	32832	1.27 (0.71 to 2.29)	0.00%	0.41	0.32
Acute Pancreatitis	5	43325	0.90 (0.51 to 1.59)	27.20%	0.24	0.63
Chronic Pancreatitis	1	9340	0.20 (0.01 to 4.17)	-	-	
Pancreatic Cancer	7	54906	1.20 (0.61 to 2.37)	24.60%	0.24	0.53
Pancreatic Event	1	4076	1.07 (0.58 to 1.96)	-	-	0.83
Cholelithiasis	2	3605	1.23 (0.84 to 1.80)	0.00%	0.90	0.09
Acute cholecystitis	1	3297	0.50 (0.15 to 1.66)	-	-	0.26
Gallbladder disorder	3	21209	1.14 (0.74 to 1.76)	11.80%	0.32	0.32

Hepatobiliary disorders	3	23409	1.12 (0.82 to 1.53)	9.00%	0.33	0.26
Alanine aminotransferase of at least 3 times the ULN	1	9432	0.57 (0.31 to 1.03)	-	-	0.06
Alanine aminotransferase of at least 5 times the ULN	1	9432	0.35 (0.14 to 0.89)	-	-	0.03*
Bilirubin of at least twice the ULN	1	9432	1.71 (0.68 to 4.35)	-	-	0.26
Hepatic Disorders	1	464	0.34 (0.01 to 8.21)	-		

Musculoskeletal

Musculoskeletal &						
Connective Tissue Disorders	2	13977	0.97 (0.39 to 2.39)	61.40%	0.11	0.72
Back Pain	3	2984	0.85 (0.61 to 1.20)	0.00%	0.56	0.18
Arthralgia	1	2248	0.94 (0.75 to 1.19)	-	-	0.62
Pain in extremity	1	2248	1.00 (0.73 to 1.36)	-	-	0.98

Ophthalmology

Eye Disorders	2	13977	1.00 (0.93 to 1.06)	0.00%	0.91	0.50
Retinopathy	1	3183	0.41 (0.17 to 0.99)	-	-	0.05*
Maculopathy	1	3183	1.67 (0.40 to 6.97)	-	-	0.48
Diabetic retinal edema	1	3183	4.00 (0.45 to 35.77)	-	-	0.21
Macular edema	1	3183	0.50 (0.15 to 1.66)	-	-	0.26
Vitreous detachment	1	3183	9.01 (0.49 to 167.13)	-	-	-
Retinal hemorrhage	1	3183	0.20 (0.01 to 4.16)	-	-	-
Retinal detachment	1	3183	3.00 (0.12 to 73.63)	-	-	-
Vitreous hemorrhage	1	3183	1.00 (0.06 to 15.98)	-	-	1.00
Retinopathy proliferative	1	3183	0.33 (0.01 to 8.18)	-	-	-
<i>Endocrinology</i>						
Endocrine Disorders	2	13977	0.94 (0.68 to 1.32)	0.00%	0.75	0.27
Thyroid C-cell						
Neoplasm/Medullary	3	38033	1.39 (0.10 to 19.69)	0.00%	0.58	0.65
Thyroid Cancer						
Thyroid Cancer	2	23477	1.21 (0.00 to 6827.68)	45.50%	0.18	0.83
Hypoglycaemia	2	9804	1.31 (0.01 to 348.44)	68.00%	0.08	0.65

Minor Hypoglycemic Event	2	4608	2.17 (1.38 to 3.43)	0.00%	0.77	0.03*
Major Hypoglycemic Event	1	4608	2.00 (0.60 to 6.62)	-	-	0.26
Symptomatic hypoglycaemia	3	1320	1.78 (1.15 to 2.74)	0.00%	0.75	0.03*
Symptomatic hypoglycaemia with blood glucose <3.3 mmol/L	2	836	1.66 (0.26 to 10.54)	0.00%	0.51	0.18
Severe symptomatic hypoglycaemia	7	36332	1.01 (0.73 to 1.40)	47.00%	0.08	0.92
Diabetic Retinopathy & Related Complications	3	16691	0.99 (0.68 to 1.44)	0.00%	0.41	0.89
Diabetic Retinopathy	3	18368	1.10 (0.58 to 2.07)	59.70%	0.08	0.58
<i>Hematology</i>						
Hematological neoplasia	1	9432	1.80 (0.60 to 5.36)	-	-	0.29

Blood and Lymphatic System Disorders	2	13977	0.98 (0.47 to 2.06)	0.00%	0.35	0.79
<i>Otolaryngology</i>						
Ear and Labyrinth Disorders	2	13977	0.92 (0.35 to 2.43)	0.00%	0.34	0.49
Nasopharyngitis	4	4154	0.91 (0.61 to 1.34)	44.60%	0.14	0.48
<i>Gynecology</i>						
Reproductive System and Breast Disorders	2	13977	1.02 (1.00 to 1.04)	0.00%	0.98	0.04*
Genital Infections	1	464	0.92 (0.42 to 2.05)	-	-	0.85
<i>Rheumatology</i>						
Severe Allergic Reactions	3	16713	1.10 (0.61 to 1.99)	24.20%	0.27	0.57
Hypersensitivity syndrome or symptoms	2	13576	0.94 (0.93 to 0.94)	0.00%	1.00	<0.01*
Immune System Disorders	2	13977	1.00 (0.51 to 1.97)	0.00%	0.73	0.96

Severe Immune						
Complex Disease	1	4076	6.50 (0.85 to 49.65)	-	-	0.07

Bolded P value ≤ 0.05 denotes statistical significance
 Legend: TEAE. Treatment-emergent adverse events;