

Supplement 3: Detailed safety analysis of the CareRA trial

	COBRA Classic	COBRA Slim (High Risk)	COBRA Avant-Garde	MTX-TSU	COBRA Slim (Low Risk)	Total
<b>Total number of AEs</b>	<b>394</b>	<b>353</b>	<b>452</b>	<b>150</b>	<b>150</b>	<b>1499</b>
<b>Total number of AEs related to therapy</b>	<b>184</b>	<b>131</b>	<b>175</b>	<b>54</b>	<b>51</b>	<b>595</b>
<b>GI tract related AEs</b>	<b>45</b>	<b>48</b>	<b>67</b>	<b>20</b>	<b>15</b>	<b>195</b>
Abdominal pain/upset	18	19	33	6	4	80
Nausea	14	16	10	9	9	58
Diarrhoea	3	4	20	3		30
Constipation	4	4	2		2	12
Reflux/heartburn	5	2		2		9
Vomiting	1	3	1			5
Flatulence			1			1
<b>General malaise related AEs</b>	<b>52</b>	<b>22</b>	<b>30</b>	<b>11</b>	<b>12</b>	<b>127</b>
Excessive warmth/sweating	11	5	5	1	1	23
Palpitations	9	3	6	2	2	22
Nervousness	6	2	9		3	20
General malaise	5	2	3	1	3	14
Fatigue	3	4	2	3	2	14
Headache	7	2	2	1		12
Vertigo	4	3		1	1	9
Insomnia	4		1			5
Shortness of breath		1		2		3
Energy loss	1		1			2
Euphoria	2					2
Migraine			1			1
<b>Liver function abnormalities</b>	<b>17</b>	<b>17*</b>	<b>22</b>	<b>6</b>	<b>3</b>	<b>65</b>
<b>Hair loss</b>	<b>7</b>	<b>10</b>	<b>16</b>	<b>3</b>	<b>5</b>	<b>41</b>
<b>infection/inflammation related AEs</b>	<b>11</b>	<b>8</b>	<b>7</b>	<b>7</b>	<b>2</b>	<b>35</b>
Respiratory infections	4*	2		1	1*	8
Cankers		2	2	3		7
Vaginal infection	1	1	2			4
Gingivitis		2		1		3
Mucositis	1				1	2
Herpes labialis	1	1				2
Herpes zoster	1					1
Throat infection				1		1
Biliary infection	1*					1
Sinusitis			1			1
Laryngitis				1		1
Tooth abscess	1					1
Genital warts			1			1
Urinary tract infection	1					1
Bacterial gastritis			1			1
<b>Changed appetite related AEs</b>	<b>18</b>	<b>3</b>	<b>9</b>		<b>4</b>	<b>34</b>
Increased appetite / weight gain	8	3	4		3	18
Decreased appetite / weight loss	5		4			9
Dry mouth	1		1		1	3
Taste of sugar in mouth	1					1
Change of taste	1					1

Numb feeling in tongue	1					1
Anorexia	1					1
<b>GC related AEs</b>	<b>9</b>	<b>5</b>	<b>7</b>			<b>21</b>
Hypertension	5	3	1			9
Cushing	3	1	3			7
Bruises	1		2			3
Polyuria			1			1
Dry skin		1				1
<b>Blood level related AEs</b>	<b>7</b>	<b>3</b>	<b>4</b>		<b>2</b>	<b>16</b>
Anaemia	2	1	3		2*	8
Leukopenia	2		1			3
Calcemia	1	1				2
Iron deficiency	2					2
Pancytopenia		1*				1
<b>Itch and Rash</b>	<b>4</b>	<b>3</b>	<b>1</b>	<b>3</b>	<b>2</b>	<b>13</b>
Skin rash	3	2		3	1	9
Allergic reaction (due to Anti TNF injection)		1			1	2
Paresthesia	1		1			2
<b>Diabetes related AEs</b>	<b>2</b>	<b>1</b>	<b>2</b>	<b>1</b>		<b>6</b>
Hyperglycaemia	1		1*	1		3
Diabetes		1				1
Impaired Glucose Tolerance	1					1
Glycosuria			1			1
<b>Visual impairment related AEs</b>		<b>1</b>		<b>1</b>	<b>2</b>	<b>4</b>
Blurred vision		1		1	1	3
Glaucoma					1	1
<b>Kidney function abnormalities</b>	<b>1</b>			<b>2</b>		<b>3</b>
<b>Miscellaneous</b>	<b>11</b>	<b>10</b>	<b>10</b>		<b>4</b>	<b>35</b>
Cramps	4		1			5
Cough	1	1	1		1	4
Flu		1	2			3
Cold			2			2
Pulmonary suffering		1	2*			3
Fever		2				2
Anal bleeding	1	1				2
Oedema	1	1				2
Slow wound healing		1	1			2
Cold feet			1			1
Pain tibiotalar		1				1
Splitted nail					1	1
Burning sensation foot	1					1
Tinnitus	1					1
Red tongue					1	1
Red face					1	1
Phlegm	1					1
Tooth extraction		1				1
Dysmenorrhea	1					1
<b>Serious AEs</b>	<b>15</b>	<b>15</b>	<b>10</b>	<b>7</b>	<b>7</b>	<b>54</b>
<b>Serious AEs related to therapy*</b>	<b>2</b>	<b>2</b>	<b>2</b>	<b>0</b>	<b>2</b>	<b>8</b>

AE= adverse event; GI= Gastro Intestinal GC= glucocorticoid; Total number of Adverse Events (related to therapy) include Serious Adverse Events (related to therapy). 1\*= 1 Serious Adverse Event related to therapy.