

Supplemental Tables

Supplemental Table 1: Cell growth inhibition test						
GODO-FAL (µg/mL)	Short term (6 h) treatment				24 h continuous treatment	
	S9 mix (-)		S9 mix (+)			
	Increase in number of cells (10 ⁴)	RPD (%)	Increase in number of cells (10 ⁴)	RPD (%)	Increase in number of cells (10 ⁴)	RPD (%)
0	235.0	100	136.3	100	201.3	100
125	197.5	90.1	125.0	94.3	180.0	93.4
250	227.5	98.1	157.5	110.1	183.8	94.6
500	208.8	98.1	138.8	101.2	158.8	86.2
1000	193.8	89.1	140.0	101.9	131.3	75.9
2000	160.0	79.0	140.0	101.9	105.0	65.0
RPD: relative population doubling						

In the chromosome aberration test, the frequencies of cells with structural aberrations were outside the range of the background data (Supplemental Table 2) for the negative control in the short term treatment with metabolic activation at the concentration of 500 µg/mL (2.3%), and in the 24 hours continuous treatment at the concentration of 2000 µg/mL (3.0%). The frequencies of cells with structural aberrations and numerical aberrations in other test substance treatments were from 0.3 to 1.0% and 0.0 to 0.8% respectively, and within the range of the background data of the negative control. Statistically meaningful difference from the respective concurrent negative controls was not observed in any test substance treatments in the frequencies of cells with structural aberrations and numerical aberrations in negative and positive control were within the range of the background data. The frequencies of cells with structural aberrations in all concurrent positive controls were increased statistically compared with the respective concurrent negative controls.

Supplemental Table 2: Background data of chromosome aberration test with cultured mammalian cells: Frequency of cells with structural aberrations (%)

Supplemental Table 3: Clinical signs of rats in the micronucleus test of GODO-FAL

Supplemental Table 4: Body weights (g) of rats in the micronucleus test of GODO-FAL					
Test substance	Dose (mg/kg)	Animal No.	1 st dosing day (Day 1)	2 nd dosing day (Day 2)	Specimen preparation day (Day 3)
Negative Control	0	1101	288	293	294
		1102	293	300	307
		1103	290	298	310
		1104	320	331	341
		1105	285	296	303
		1106	307	316	326
		Mean	297.2	305.7	313.5
		SD	13.6	14.8	17.1
GODO-FAL	500	1201	303	314	317
		1202	298	309	316
		1203	311	316	321
		1204	283	296	304
		1205	276	280	287
		1206	295	302	306
		Mean	294.3	302.8	308.5
		SD	12.9	13.5	12.4
	1000	1301	290	306	308
		1302	309	319	331
		1303	301	311	318
		1304	290	301	308
		1305	300	317	323
		1306	284	297	308
		Mean	295.7	308.5	316.0
		SD	9.2	8.8	9.7
	2000	1401	283	298	303
		1402	310	323	331
		1403	307	321	327
		1404	294	305	310
		1405	294	302	310
		1406	295	304	310
		Mean	297.2	308.8	315.2
		SD	9.9	10.5	11.1
Positive Control (CP)	20	1501	Not recorded	312	310
		1502	Not recorded	326	325
		1503	Not recorded	292	293
		1504	Not recorded	304	309
		1505	Not recorded	309	307
		1506	Not recorded	302	304
		Mean	-	307.5	308.0
		SD	-	11.4	10.4
Negative control: water for injection (Japanese Pharmacopeia) Positive control group (CP, cyclophosphamide), dosed at 2 nd day (1 st dosing) No significant difference was found between the vehicle control and GODO-FAL treated groups by Dunnett's test.					

Supplemental Table 5: Background data for micronucleus test in rats:						
Treatment	Number of tests	Min	Max	Mean	SD	Variation range (%)
<i>Frequency of micronucleated immature erythrocytes (%)</i>						
Negative Control	17	0.05	0.33	0.15	0.07	0.01-0.29
Positive Control CP 20 mg/kg	9	2.25	3.75	3.09	0.52	2.05-4.13
<i>Ratio of immature erythrocyte to total erythrocytes (%)</i>						
Negative Control	17	47.7	64.7	54.7	3.9	46.9-62.5
Positive Control CP 20 mg/kg	9	32.7	52.4	45.3	6.0	33.3-57.3
Standard of background data on negative control values and positive control values, from 2007 to March 2016. Animal: Rats of CrI:SD, male, 8 weeks old. Variation range: Mean $\pm$ standard deviation (SD) If the calculated value is less than zero or equal to zero, the minimum value is regarded as the lower limit Positive Control: CP, cyclophosphamide						

Supplemental Table 6: Body weights in rats after a single administration of GODO-FAL							
Animal No	Time after administration (Day)						Body weight gain
	0	1	2	4	7	14	
2101	217	241	233	249	254	268	51
2102	209	235	238	240	257	285	76
2103	204	222	216	237	239	253	49
2104	201	223	228	237	235	264	63
2105	191	209	214	223	225	249	58
Mean $\pm$ SD	204 $\pm$ 10	226 $\pm$ 12	226 $\pm$ 10	237 $\pm$ 9	242 $\pm$ 13	264 $\pm$ 14	59 $\pm$ 11

Supplemental Table 7: Urinalysis results in male and female rats in the 90-day oral toxicity study of GODO-FAL																
Treatment groups	pH	No. rats	Protein	No. Rats	Glucose	No. rats	Ketone	No. rats	Urobilinogen	No. rats	Bilirubin	No. rats	Occult Blood	No. rats	RBC	No. rats
Males n=5/treatment group																
0 (Control)	6.0	0	-	2	-	5	-	1	-	0	-	5	-	5	-	5
	6.5	0	±	2	±	0	±	2	±	5	±	0	±	0	±	0
	7.0	0	+	1	+	0	+	2	+	0	+	0	+	0	+	0
	7.5	0	++	0	++	0	++	0	++	0	++	0	++	0	++	0
	8.0	0	+++	0	+++	0	+++	0	+++	0	+++	0	+++	0	+++	0
	8.5	5	4+	0	4+	0	4+	0	+++	0	+++	0	+++	0	+++	0
2000	6.0	0	-	2	-	5	-	2	-	0	-	5	-	5	-	5
	6.5	0	±	1	±	0	±	2	±	5	±	0	±	0	±	0
	7.0	0	+	2	+	0	+	1	+	0	+	0	+	0	+	0
	7.5	0	++	0	++	0	++	0	++	0	++	0	++	0	++	0
	8.0	0	+++	0	+++	0	+++	0	+++	0	+++	0	+++	0	+++	0
	8.5	5	4+	0	4+	0	4+	0	+++	0	+++	0	+++	0	+++	0
Females n=5/treatment group																
0 (Control)	6.0	0	-	5	-	5	-	5	-	0	-	5	-	5	-	5
	6.5	0	±	0	±	0	±	0	±	5	±	0	±	0	±	0
	7.0	0	+	0	+	0	+	0	+	0	+	0	+	0	+	0
	7.5	0	++	0	++	0	++	0	++	0	++	0	++	0	++	0
	8.0	0	+++	0	+++	0	+++	0	+++	0	+++	0	+++	0	+++	0
	8.5	5	4+	0	4+	0	4+	0	+++	0	+++	0	+++	0	+++	0
2000	6.0	0	-	4	-	5	-	5	-	0	-	5	-	5	-	5
	6.5	0	±	1	±	0	±	0	±	5	±	0	±	0	±	0
	7.0	0	+	0	+	0	+	0	+	0	+	0	+	0	+	0
	7.5	0	++	0	++	0	++	0	++	0	++	0	++	0	++	0
	8.0	1	+++	0	+++	0	+++	0	+++	0	+++	0	+++	0	+++	0
	8.5	4	4+	0	4+	0	4+	0	+++	0	+++	0	+++	0	+++	0

Supplemental Table 8: Urinalysis results in male and female rats in the 90-day oral toxicity study of GODO-FAL																
Treatment groups	WBC	No. Rats	Epithelial Cells	No. Rats	Granular Cast	No. Rats	Hyaline Cast	No. Rats	Cylindroid	No. Rats	AMP	No. Rats	AP	No. Rats	CO	No. Rats
Males n=5/treatment group																
0 (Control)	-	4	-	0	-	5	-	5	-	5	-	3	-	5	-	5
	±	1	±	5												
	+	0	+	0												
	++	0	++	0												
	+++	0	+++	0												
2000	-	4	-	0	-	5	-	5	-	5	-	2	-	5	-	5
	±	1	±	5												
	+	0	+	0												
	++	0	++	0												
	+++	0	+++	0												
Females n=5/treatment group																
0 (Control)	-	5	-	0	-	5	-	5	-	5	-	4	-	5	-	5
	±	0	±	5												
	+	0	+	0												
	++	0	++	0												
	+++	0	+++	0												
2000	-	4	-	0	-	5	-	5	-	5	-	3	-	5	-	5
	±	1	±	5												
	+	0	+	0												
	++	0	++	0												
	+++	0	+++	0												

Supplemental Table 9: Urinalysis results in male and female rats in the 90-day oral toxicity study of GODO-FAL								
Treatment Group	CC	No. rats	Others	No. rats	Color	No. rats	Cloudy	No. rats
Males n=5/treatment group								
0 (Control)	- +	5 0	- +	5 0	PY Y PBY BY AU R RB PR	2 2 1 0 0 0 0 0	- +	5 0
2000	- +	5 0	- +	5 0	PY Y PBY BY AU R RB PR	2 2 1 0 0 0 0 0	- +	5 0
Females n=5/treatment group								
0 (Control)	- +	5 0	- +	5 0	PY Y PBY BY AU R RB PR	4 1 0 0 0 0 0 0	- +	5 0
2000	- +	5 0	- +	5 0	PY Y PBY BY AU R RB PR	4 1 0 0 0 0 0 0	- +	5 0

Supplemental Table 10: Urinalysis results in male and female rats in the 90-day oral toxicity study of GODO-FAL								
Treatment group	Volume (mL)	Specific Gravity(g/cm ³)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	Na excretion (mg)	K excretion (mg)	Cl excretion (mg)
Males n=5/treatment group								
0 (Control)	16.6 ± 4.7	1.05 ± 0.010	89 ± 29	210.5 ± 51.9	148 ± 43	33 ± 9	131 ± 20	83 ± 19
2000	17.4 ± 5.2	1.05 ± 0.013	115 ± 36	235.9 ± 64.9	173 ± 52	43 ± 8	151 ± 13	100 ± 11
Females n=5/treatment group								
0 (Control)	13.9 ± 6.0	1.04 ± 0.013	103 ± 22	204.0 ± 58.1	157 ± 38	31 ± 10	100 ± 20	72 ± 16
2000	11.6 ± 4.3	1.04 ± 0.016	118 ± 54	204.3 ± 93.4	165 ± 80	28 ± 5	83 ± 18	61 ± 15

