SUPPLEMENTAL MATERIAL

eTable1: Study medication (fasiglifam, placebo or active drug) stopping criteria

<table>
<tr><th colspan="4">Stopping criteria</th></tr>
<tr><td rowspan="4">For all trials except TAK 875_306</td><td rowspan="4">- ALT or AST > 8x ULN
- ALT or AST > 5x ULN for > 2 weeks
- ALT or AST > 3x ULN and (total bilirubin [TBL] > 2xULN or international normalized ratio [INR] >1.5xULN)
- ALT or AST > 3xULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)
- Elevation of TBL >2.0xULN on repeated testing after initial TBL > 2.0x ULN
- Elevation of ALP to ≥ 3xULN on repeat testing after initial ALP elevation ≥ 1.5xULN</td><td colspan="2">TAK 875_306</td></tr>
<tr><td>Normal or elevated ALT or AST at baseline (all participants)</td><td>- ALT or AST >8x ULN</td></tr>
<tr><td>Normal ALT or AST at baseline</td><td>- ALT or AST >5x ULN and persists for more than 2 weeks
- ALT or AST >3x ULN in conjunction with elevated total bilirubin >2x ULN or INR >1.5
- ALT or AST >3x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)</td></tr>
<tr><td>Elevated ALT or AST at baseline</td><td>- ALT or AST >5x ULN and 2-fold increases above baseline values and persists for more than 2 weeks
- ALT or AST >5x ULN and 2-fold increases above baseline values in conjunction with elevated total bilirubin >2 ULN or INR >1.5
- ALT or AST >5x ULN and 2-fold increases above baseline values with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)</td></tr>
<tr><td colspan="4">Additional criteria for study mediation withdrawal:
– Elevation of TBL >2.0xULN on repeated testing after initial TBL > 2.0x ULN
– Elevation of ALP to ≥ 3xULN on repeat testing after initial ALP elevation ≥ 1.5xULN</td></tr>
</table>

eTable 2: Summary of liver toxicity in the eight clinical trials within the fasiglifam development program

Study	Parameter	Fasiglifam 25mg n (%)	Fasiglifam 50mg n (%)	Placebo n (%)	Glimepiride n (%)	Sitagliptin n (%)
301	Randomized as of cut off	137	141	143		
	Safety population	137 (100%)	141 (100%)	143 (100%)		
	Median duration of drug exposure, months	5.7 (5.6, 5.7)	5.6 (5.6, 5.7)	5.7 (5.6, 5.7)		
	Duration of exposure (patient-years)	61.5	61.8	63.4		
	ALT or AST >3xULN	5 (3.6%)	4 (2.8%)	1 (0.7%)		
	ALT or AST >5xULN	1 (0.7%)	3 (2.1%)	0		
	ALT or AST >8xULN	1 (0.7%)	2 (1.4%)	0		
	ALT or AST >10xULN	1 (0.7%)	2 (1.4%)	0		
	Hy's Law Cases	0	0	0		
302	Randomized as of cut off	262	261	132		260
	Safety population	259 (100%)	261 (100%)	131 (100%)		260 (100%)
	Median duration of drug exposure, months	5.6 (2.9, 7.0)	5.6 (2.7, 7.0)	5.6 (2.3, 7.1)		5.6 (2.8, 7.7)
	Duration of exposure (patient-years)	119.7	117.1	57.7		124.8
	ALT or AST >3xULN	8 (3.1%)	4 (1.5%)	3 (2.3%)		4 (1.5%)
	ALT or AST >5xULN	4 (1.5%)	2 (0.8%)	0		2 (0.8%)
	ALT or AST >8xULN	2 (0.8%)	2 (0.8%)	0		2 (0.8%)
	ALT or AST >10xULN	1 (0.4%)	2 (0.8%)	0		1 (0.4%)
	Hy's Law Cases	0	0	0		2 (0.8%)
303	Randomized as of cut off	31	29	30		
	Safety population	31 (100%)	29 (100%)	30 (100%)		
	Median duration of drug exposure, months	2.8 (0.9, 3.8)	2.1 (1.0, 3.1)	2.2 (0.8, 3.8)		
	Duration of exposure (patient-years)	6.3	5.7	6.0		
	ALT or AST >3xULN	0	0	0		
	ALT or AST >5xULN	0	0	0		
	ALT or AST >8xULN	0	0	0		
	ALT or AST >10xULN	0	0	0		
	Hy's Law Cases	0	0	0		
304	Randomized as of cut off	817	813		824	
	Safety population	817 (100%)	813 (100%)		824 (100%)	
	Median duration of drug exposure	10.8 (6.5, 14.3)	10.8 (6.2, 13.9)		10.8 (6.2, 13.9)	
	Duration of exposure (patient-years)	716.0	699.4		708.8	
	ALT or AST >3xULN	29 (3.5%)	44 (5.4%)		10 (1.2%)	
	ALT or AST >5xULN	10 (1.2%)	18 (2.2%)		3 (0.4%)	
	ALT or AST >8xULN	5 (0.6%)	7 (0.9%)		1 (0.1%)	
	ALT or AST >10xULN	3 (0.4%)	6 (0.7%)		1 (0.1%)	
	Hy's Law Cases	0	2 (0.2%)		0	

306	Randomized as of cut off		1599	1602		
	Safety population		1597 (100%)	1602 (100%)		
	Median duration of drug exposure, months		9.3 (4.2, 11.3)	9.3 (4.1, 11.5)		
	Duration of exposure (patient-years)		1104.8	1110.6		
	ALT or AST >3xULN		35 (2.2%)	10 (0.6%)		
	ALT or AST >5xULN		22 (1.4%)	2 (0.1%)		
	ALT or AST >8xULN		11 (0.7%)	1 (0.1%)		
	ALT or AST >10xULN		9 (0.6%)	1 (0.1%)		
	Hy's Law Cases		0	0		
307	Randomized as of cut off	131	130	131		
	Safety population	130 (100%)	130 (100%)	131 (100%)		
	Median duration of drug exposure, months	4.6 (1.9, 5.6)	4.7 (2.0, 5.6)	4.3 (1.2, 5.6)		
	Duration of exposure (patient-years)	41.3	41.5	38.7		
	ALT or AST >3xULN	1 (0.8%)	4 (3.1%)	1 (0.8%)		
	ALT or AST >5xULN	1 (0.8%)	3 (2.3%)	0		
	ALT or AST >8xULN	1 (0.8%)	3 (2.3%)	0		
	ALT or AST >10xULN	1 (0.8%)	3 (2.3%)	0		
	Hy's Law Cases	1 (0.8%)	2 (1.5%)	0		
309	Randomized as of cut off		16	17		
	Safety population		16 (100%)	17 (100%)		
	Median duration of drug exposure, months		0.9 (0.6, 1.6)	1.3 (0.9, 2.1)		
	Duration of exposure (patient-years)		1.8	2.6		
	ALT or AST >3xULN		0	0		
	ALT or AST >5xULN		0	0		
	ALT or AST >8xULN		0	0		
	ALT or AST >10xULN		0	0		
	Hy's Law Cases		0	0		
310	Randomized as of cut off		50		46	
	Safety population		50 (100%)		46 (100%)	
	Median duration of drug exposure, months		2.0 (1.0, 2.9)		2.2 (1.1, 4.5)	
	Duration of exposure (patient-years)		9.2		9.8	
	ALT or AST >3xULN		0		0	
	ALT or AST >5xULN		0		0	
	ALT or AST >8xULN		0		0	
	ALT or AST >10xULN		0		0	
	Hy's Law Cases		0		0	

Samples sizes for studies 301, 302, 303, 304, 306, 307, 309 and 310 based on IVRS data as of cut-off 10Feb2014
Hy's Law cases are defined as ALT or AST > 3x ULN with bilirubin > 2x ULN in the absence of cholestasis and an alternative explanation
ALT indicates alanine transaminase, AST aspartate transaminase, ULN upper limit normal

eTable 3: Summary of the major adverse cardiovascular event composite and all-cause death

				Active Control / Placebo				
Parameter	**Study**	**Fasiglifam 25mg**	**Fasiglifam 50mg**	**Placebo**	**Glimepiride**	**Sitagliptin**	**Overall**	**RR[B] (95%CI)**
MACE composite, n (%)	301	0 / 0	1 / 141 (0.7)	0 / 0			1 / 421 (0.2)	
	302	3 / 259 (1.2)	0 / 0	0 / 0		0 / 0	3 / 911 (0.3)	
	303	0 / 0	0 / 0	0 / 0			0 / 0	
	304	3 / 817 (0.4)	7 / 813 (0.9)		7 / 824 (0.8)		17 / 2454 (0.7)	
	306		24 / 1597 (1.5)	28 / 1602 (1.7)			52 / 3199 (1.6)	
	307	0 / 0	0 / 0	1 / 131 (0.8)			1 / 391 (0.3)	
	309		0 / 0	0 / 0			0	
	310		0 / 0			0 / 0	0 / 0	
	Total	6 /1374 (0.4)	32 / 3037 (1.1)	29 / 2054 (1.4)	7 / 824 (0.8)	0 / 0	74 / 7595 (1.0)	0.76 (0.48, 1.20)
All-cause death, n (%)	301	0 / 0	1 / 141 (0.7)	0 / 0			1 / 421 (0.2)	
	302	0 / 0	0 / 0	1 / 131 (0.8)		1 / 260 (0.4)	2 / 911 (0.2)	
	303	0 / 0	0 / 0	0 / 0			0	
	304	4 / 817 (0.5)	4 / 813 (0.5)		5 / 824 (0.6)		13 / 2454 (0.5)	
	306		12 / 1597 (0.8)	17 / 1602 (1.1)			29 / 3199 (0.9)	
	307	0 / 0	1 / 130 (0.8)	0 / 0			1 / 391 (0.3)	
	309		0 / 0	0 / 0			0 / 0	
	310		0 / 0			0 / 0	0 / 0	
	Total	4 / 1374 (0.3)	18 / 3037 (0.6)	18 / 2054 (0.9)	5 / 824 (0.6)	1 / 306 (0.3)	46 / 7595 (0.6)	0.66 (0.37, 1.18)

[a]Fasiglifam versus Active control / Placebo using Mantel-Haenszel method

MACE represents major adverse cardiovascular event (composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke and hospitalization for unstable angina); RR, relative risk

ALT indicates alanine transaminase, AST aspartate transaminase, INR international normalized ratio, TBL, total bilirubin, ULN upper limit normal

eTable 4: Summary of the accumulated liver function disorder cases adjudicated by the Liver Safety Evaluation Committee (LSEC)

Parameter	Studies 301, 302, 303, 304, 306, 307, 309 & 310 Fasiglifam-25mg (N=1378)	Studies 301, 302, 303, 304, 306, 307, 309 & 310 Fasiglifam-50mg (n=3039)	Japan phase 3 studies CCT-003, OCT-002 & OCT-003 Fasiglifam 25mg & 50mg (N=1681)	All Studies[a] Placebo or Other Treatment (N=3252)	Total (N=9350)
Number of hepatic disorder cases LSEC reviewed	14 (1.02%)	39 (1.28%)	14 (0.83%)	8 (0.25%)	75 (0.80%)
LSEC Adjudication regarding DILI[b]					
Highly Likely	0	1 (0.03%)	0	0	1 (0.01%)
Probable	11 (0.80%)	24 (0.79%)	3 (0.18%)	2 (0.06%)	40 (0.43%)
Possible	2 (0.15%)	8 (0.26%)	7 (0.42%)	2 (0.06%)	19 (0.20%)
Excluded/Unrelated/ Unlikely	1 (0.07%)	6 (0.20%)	4 (0.24%)	4 (0.12%)	15 (0.16%)

Sample size for the Japan studies are based on communication as of 22Oct2013. Samples sizes for studies 301, 302, 303, 304, 306, 307, 309 and 310 based on IVRS data as of cut-off 10Feb2014

N indicates number of particpants randomized. The number of participants randomized in each treatment group (N) is used as the denominator for percentage calculations

[a] Includes Japan phase 3 studies

[b] DILI, indicates drug-induced liver injury