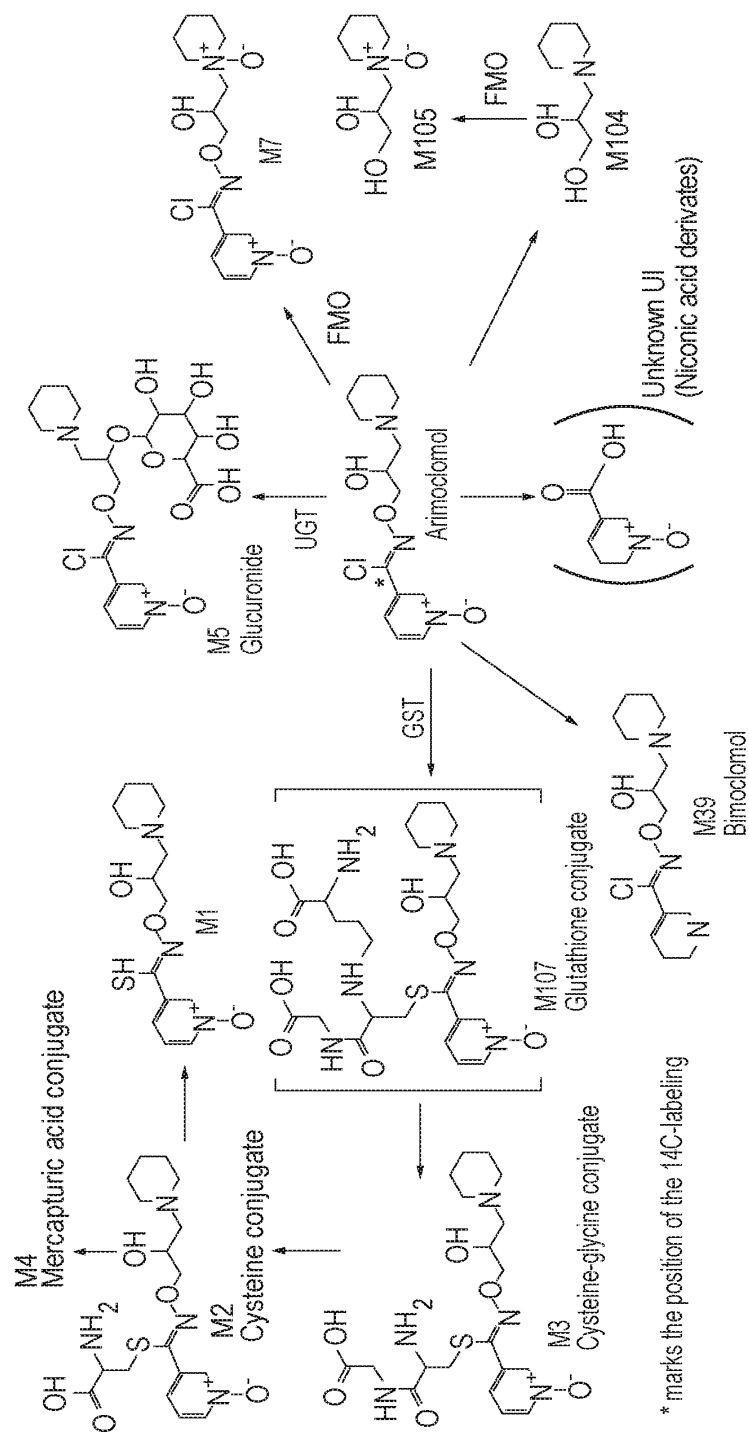




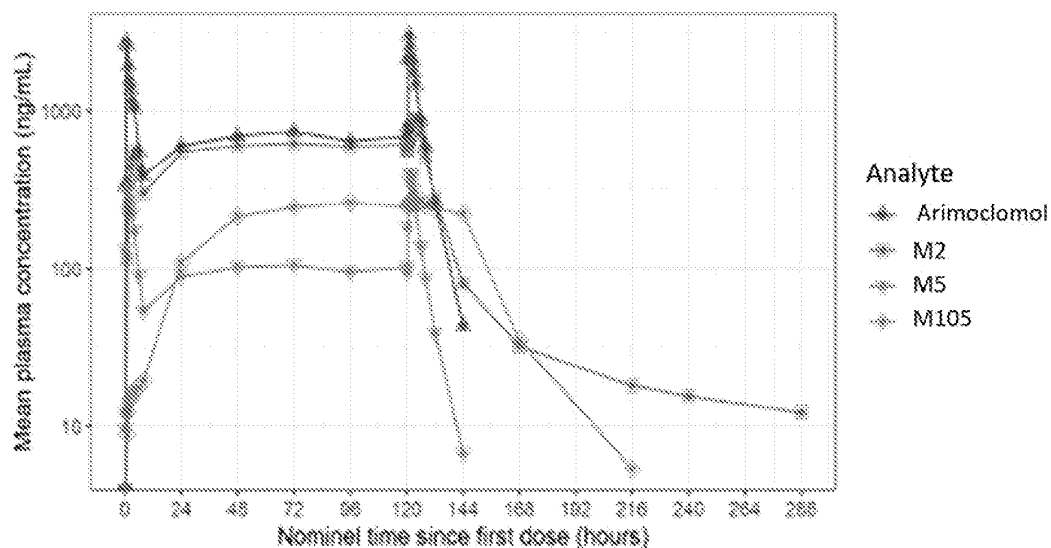
7
8
9
10
11

Sample	Mean 1-6	Mean 7-12	RSD 1-6	RSD 7-12	p-value (t-test)	t2
8106X, pH 6.8	98.5	89.8	14.3	24.8	0.01388	32.4
8652X, pH 1.2	72.7	94.4	17.1	13.8	0.04848	38.8

Table 41: Comparison of test data obtained from vessel 1-6 vs. vessel 7-12

FIG. 2

Figure 2-3 Mean Plasma Concentrations of Arimoclomol and its Metabolites M2, M5, and M105 following Multiple-Doses of 248 mg t.i.d. – Trial OR-ARI-MET-01



Source: {OR-ARI-MET-01, Listings 16.2.5.2 and 16.2.5.3}

FIG. 3

Table 2-5 Single- and Multiple-Dose Pharmacokinetic Parameters of Arimoclomol metabolites M2, M5 and M105 in Male Subjects -- Trial OR-ARI-MET-01

Parameter/ Analyte	148 mg SD			248 mg t.i.d. (744 mg/day)		
	Day 1			Day 6		
	N=6			N=6		
	M2	M5	M105	M2	M5	M105
AUC _{0-∞} (h ng/mL)	3774 ^a (NA)	1275 (25)	135 ^a (NA)	5632 (24)	1789 (18)	2010 (32)
AUC ₀₋₈ (h ng/mL)	5892 ^a (NA)	1462 (22)	NA ^a	-	-	-
C _{max} (ng/mL)	547 (17)	336 (34)	19.2 (28)	892 (22)	446 (20)	277 (32)
t _{max} (h)	4.6 (3.0,4.0)	1.3 (1.0,2.5)	8.0 ^a (2.5,8.0)	3.5 (2.5,4.0)	1.5 (1.0,2.0)	6.0 ^a (3.0,8.0)
t _{1/2} (h)	4.2 ^a (NA)	2.4 (14)	NA ^a	96.8 (9)	3.5 (17)	12.9 (12) ^a
AR	-	-	-	1.62 ^a (NA)	1.4 (15)	16.3 (NA) ^a
MR (AUC)	0.42 ^a (11)	0.15 (33)	0.04 ^a (34)	0.61 (10)	0.16 (28)	0.50 (37)
MR (C _{max})	0.25 (43)	0.12 (49)	0.02 (32)	0.34 (24)	0.14 (16)	0.24 (37)

Geometric mean (geometric CV%) values are presented for all parameters except t_{max}. Median (min,max) values are presented for t_{max}. AR=Accumulation Ratio. MR=Metabolic Ratio based on either AUC or C_{max}. Example of MR formula: MR (AUC) SD = (AUC_{Metabolite}/MW Metabolite) / (AUC_{Parent}/MW Parent). NA= Not Applicable

^a not estimable in 3 subjects

^b Not estimable in 6 subjects

^c Not reportable in 1 subject due to the adjusted R² < 0.7

^d 8 hours sample last sample in profile

^e Based on AUC_{0-∞}

Source: [OR-ARI-MET-01, Sections 11.4.5, 11.4.6, 11.4.7].

FIG. 4

Table 11-2: Summary Statistics of Plasma Pharmacokinetic Parameters of M2 Following the Therapeutic Dose (200 mg) of Arimocloamol TID (Treatment A) on Days 1 and 3

Day	Parameter*	N	AM	SD	Min	Median	Max	CV%	GM	GCV%
1	C _{max} , ng/mL	34	299	64.7	193	291	448	21.6	292	21.4
	T _{max} , h ²	34	--	--	2.59	4.08	6.08	--	--	--
	AUC ₀₋₈ , h*ng/mL	34	1520	343	892	1470	2360	22.5	1480	22.6
	AUC ₀₋₄ , h*ng/mL	34	1520	343	892	1470	2360	22.6	1480	22.6
	MR _{C_{max}}	34	0.322	0.102	0.162	0.307	0.606	31.6	0.307	32.1
	MR _{AUC}	34	0.496	0.0736	0.325	0.470	0.655	15.0	0.484	14.9
3	C _{max} , ng/mL	34	535	144	315	509	947	27.0	517	26.9
	T _{max} , h ²	34	--	--	2.59	3.50	5.00	--	--	--
	C _{max} , ng/mL	34	271	86.3	140	240	481	31.8	259	30.9
	AUC ₀₋₈ , h*ng/mL	34	3210	869	1850	3060	5690	27.1	3100	26.2
	AUC ₀₋₂₄ , h*ng/mL	34	5260	1620	2970	4740	10600	30.9	5050	28.7
	AUC ₀₋₆ , h*ng/mL	34	5260	1630	2970	4740	10600	30.9	5050	28.7
	ke, 1/h	34	0.124	0.0135	0.100	0.120	0.154	10.8	0.124	10.6
	t _{1/2} , h	34	5.63	0.587	4.50	5.76	6.93	10.4	5.60	10.6
	RacObs	34	2.13	0.431	1.48	2.06	3.94	20.3	2.09	17.9
	MR _{C_{max}}	34	0.460	0.120	0.228	0.452	0.777	26.2	0.444	27.3
	MR _{AUC}	34	0.727	0.133	0.551	0.706	1.04	18.2	0.716	17.6

AM: Arithmetic Mean; SD: Standard Deviation; Min: Minimum; Max: Maximum; GM: Geometric Mean; CV%: Arithmetic CV which is equal to SD/AM*100; GCV%: Geometric CV which is equal to 100 x sqrt (exp (s²) - 1), where s² is the observed variance on the natural log-scale.
2: Median (min, max) reported for T_{max}.
RacObs: Accumulation ratio was calculated as: AUC_{0-8, Day 3}/AUC_{0-8, Day 1}.
*: For all subjects on Day 1, t_{1/2}, ke, and AUC₀₋₂₄ were not estimable due to undetermined ke or not reportable due to %AUC₀₋₂₄ >20%.

FIG. 5

Table 11-5: Summary Statistics of Plasma Pharmacokinetic Parameters of M2 Following the Supratherapeutic Dose (600) mg) of Arimoclomol TID (Treatment B) on Days 1 and 3

Day	Parameter*	N [‡]	AM	SD	Min	Median	Max	CV% [§]	GM	GCV% [§]
1	C _{max} , ng/mL	34	993	199	650	963	1370	20.1	973	20.8
	T _{max} , h [¶]	34	--	--	3.00	4.00	6.00	--	--	--
	AUC ₀₋₆ , h*ng/mL	34	5100	1060	3090	5050	7110	20.7	4990	21.7
	AUC _{0-∞} , h*ng/mL	34	5090	1060	3090	5050	7110	20.7	4980	21.7
	MR _{C_{max}}	34	0.326	0.0794	0.212	0.315	0.489	24.4	0.317	24.4
	MR _{AUC}	34	0.476	0.0763	0.363	0.462	0.662	16.0	0.471	15.5
3	C _{max} , ng/mL	34	1690	398	915	1680	2740	23.5	1650	24.1
	T _{max} , h [¶]	34	--	--	0.52	4.00	5.00	--	--	--
	C _{min} , ng/mL	34	898	218	542	883	1460	24.3	873	24.3
	AUC ₀₋₆ , h*ng/mL	34	10290	2180	6260	10300	15100	21.4	9930	21.8
	AUC ₀₋₂₄ , h*ng/mL	34	16800	4100	10900	16700	27700	24.3	16400	23.8
	AUC _{0-∞} , h*ng/mL	34	16800	4100	10900	16700	27700	24.3	16400	23.8
	ke, 1/h	33	0.139	0.0138	0.112	0.127	0.168	10.6	0.129	10.3
	t _{1/2} , h	33	5.40	0.539	4.18	5.46	8.19	10.0	5.37	10.3
	RacObs	34	2.01	0.238	1.38	2.01	2.45	11.9	1.99	12.5
	MR _{C_{max}}	34	0.444	0.116	0.286	0.427	0.807	26.2	0.431	24.9
	MR _{AUC}	34	0.703	0.110	0.551	0.674	0.992	15.7	0.695	15.1

AM: Arithmetic Mean, SD: Standard Deviation, Min: Minimum, Max: Maximum, GM: Geometric Mean, CV%: Arithmetic CV which is equal to STD/AM*100; GCV%: Geometric CV which is equal to 100 x sqrt (exp (s²) - 1), where s² is the observed variance on the natural log-scale.
‡: Median (min, max) reported for T_{max}.
RacObs: Accumulation ratio was calculated as AUC_{0-24, Day 3}/AUC_{0-6, Day 1}.
*: For all subjects on Day 1, t_{1/2}, ke, and AUC_{0-∞} were not estimable due to undetermined ke or not reportable due to %AUC_{extrop} >20%.
‡: t_{1/2} and ke were not estimable for 1 subject on Day 3 due to undetermined ke.

FIG. 6

Table 11-3: Summary Statistics of Plasma Pharmacokinetic Parameters of M105 Following the Therapeutic Dose (200 mg) of Arimoclomol TID (Treatment A) on Days 1 and 3

Day	Parameter**	N*	AM	SD	Min	Median	Max	CV%	GM	GCV%
1	C _{max} , ng/mL	29	12.4	6.16	5.41	11.1	37.6	49.6	11.4	41.8
	T _{max} , h [‡]	29	--	--	2.50	7.83	8.05	--	--	--
	AUC ₀₋₄ , h*ng/mL	29	59.2	28.1	7.59	60.9	115	47.5	49.5	81.9
	AUC ₀₋₂₄ , h*ng/mL	29	59.2	28.1	7.59	60.9	115	47.5	49.5	82.0
	MR _{Cmax}	29	0.0308	0.0155	0.0112	0.0275	0.0627	50.4	0.0275	59.3
	MR _{AUC}	29	0.0451	0.0220	0.00425	0.0453	0.0939	48.8	0.0371	89.4
3	C _{max} , ng/mL	34	129	32.7	77.6	111	215	27.3	118	26.3
	T _{max} , h [‡]	34	--	--	0.00	4.06	8.00	--	--	--
	C _{min} , ng/mL	34	92.0	27.6	47.9	84.9	167	30.0	88.2	30.0
	AUC ₀₋₈ , h*ng/mL	34	859	236	539	837	1540	27.5	836	26.6
	AUC ₀₋₂₄ , h*ng/mL	34	2570	737	1439	2490	4498	28.7	2470	28.0
	AUC ₀₋₄ , h*ng/mL	34	2570	739	1440	2490	4420	28.8	2470	28.0
	RacObs	29	35.7	33.2	6.68	33.0	142	129.0	17.0	93.6
	MR _{Cmax}	34	0.243	0.0946	0.0876	0.248	0.549	38.9	0.227	40.5
	MR _{AUC}	34	0.455	0.140	0.264	0.421	0.782	30.8	0.435	39.3

AM: Arithmetic Mean; SD: Standard Deviation; Min: Minimum; Max: Maximum; GM: Geometric Mean; CV%: Arithmetic CV which is equal to $STD/AM*100$; GCV%: Geometric CV which is equal to $100 \times \sqrt{(\exp(s^2) - 1)}$, where s^2 is the observed variance on the natural log-scale.

[‡]: Median (min, max) reported for T_{max}.

RacObs: Accumulation ratio was calculated as $AUC_{0-8, Day 3}/AUC_{0-8, Day 1}$.

^{*}: PK parameters of M105 for 5 subjects were not estimable because the entire concentration-time profile was <LLOQ on Day 1.

^{**}: t_{1/2}, t_{1/2}, t_{1/2}, and AUC_{0-inf} for M105 could not be estimated for any profiles, as terminal phase was not reached on Days 1 and 3.

FIG. 7

Table 11-6: Summary Statistics of Plasma Pharmacokinetic Parameters of M105 Following the Supratherapeutic Dose (600) mg) of Arimoclomol TID (Treatment B) on Days 1 and 3

Day	Parameter [†]	N	AM	SD	Min	Median	Max	CV%	GM	GCV%
1	C _{max} , ng/mL	34	26.8	9.86	9.01	26.9	49.5	36.8	24.9	43.0
	T _{max} , h [±]	34	--	--	3.50	8.00	8.02	--	--	--
	AUC ₀₋₈ , h*ng/mL	34	131	63.6	20.9	135	280	48.6	113	67.9
	AUC _{0-∞} , h*ng/mL	34	131	63.6	20.9	135	280	48.5	113	67.8
	MR _{C_{max}}	34	0.0205	0.00918	0.00496	0.0187	0.0435	44.7	0.0184	53.1
	MR _{AUC}	34	0.0286	0.0147	0.00396	0.0270	0.0697	51.6	0.0241	72.9
3	C _{max} , ng/mL	34	389	120	208	359	800	30.9	373	30.1
	T _{max} , h [±]	34	--	--	0.00	3.50	8.00	--	--	--
	C _{min} , ng/mL	34	293	101	129	269	633	34.3	277	35.0
	AUC ₀₋₈ , h*ng/mL	34	2760	862	1340	2540	5600	31.2	2640	31.3
	AUC ₀₋₂₄ , h*ng/mL	34	8430	2550	4880	8100	18300	30.2	8110	27.8
	AUC _{0-∞} , h*ng/mL	34	8440	2550	4880	8110	18300	30.2	8130	27.7
	RacObs	34	30.5	29.3	8.77	20.2	160	95.9	23.4	76.9
	MR _{C_{max}}	34	0.246	0.126	0.0999	0.213	0.748	51.3	0.222	47.4
	MR _{AUC}	34	0.449	0.168	0.193	0.412	0.845	37.4	0.420	39.3

AM: Arithmetic Mean; SD: Standard Deviation; Min: Minimum; Max: Maximum; GM: Geometric Mean; CV%: Arithmetic CV which is equal to STD/AM*100; GCV%: Geometric CV which is equal to 100 x sqrt (exp (s²) - 1), where s² is the observed variance on the natural log-scale.
±: Median (min, max) reported for T_{max}.
RacObs: Accumulation ratio was calculated as AUC_{0-24, Day 3} / AUC_{0-24, Day 1}.
† : t_{1/2}, k_e, and AUC_{0-∞} for M105 could not be estimated for any profiles, as terminal phase was not reached on Days 1 and 3.

FIG. 8

Table 3-4 Dose Proportionality of Arimoclomol Following Multiple t.i.d. Administration – Pooled Data from Trials AALS-003, AALS-010, and OR-ARI-MET-01

Parameter (Units)	Dose Range	Slope	Slope (99% CI)
C_{max} (ng/mL)	63 to 372 t.i.d.	1.11	1.03 – 1.21
	(386 to 1116 mg/day)		
AUC ₀₋₁₂ (ng·h/mL)	63 to 372 t.i.d.	1.17	1.08 – 1.25
	(386 to 1116 mg/day)		

Source: Appendix, Table 6-3.
Dose proportionality assessments were performed by statistical analysis using a power model.

FIG. 9

Table 3-3

Arimocicamol Oral Clearance Following Single Dosing and
Multiple i.i.d. Oral Dosing of 31 to 372 mg - Trials 40339 (BRX-
345 CLT P1-002), AALS-005, AALS-010, and OR-ARI-MET-01

Trial	Population	Dose mg i.i.d. (mg/day)	N	CLT (L/h) SD (Day 1 of dosing)	CLT (L/h) SD (Last day of dosing)
AALS-005	Men	62 (180)	7	60.6 (16)	72.0 (19) ^a
	Men	124 (372)	7	43.3 (20)	39.0 (22) ^a
	Men	168 (744)	7	31.8 (24)	43.4 (37) ^a
	Men	372 (1116)	7	43.4 (8)	57.7 (30) ^a
OR-ARI-MET-01	Young men	168 (744)	6	39.7 (17)	34.3 (18) ^a
AALS-010	Men	168 (744)	12 ^a	43.2 (35)	37.4 (17) ^a

Source: Trials {40339, AALS-005, AALS-010, OR-ARI-MET-01}
Geometric mean (geometric CV%) values are presented.
^aOne subject withdrew on Day 11 and therefore was not included in the PK analysis for Day 28.
^aDay 5
^aDay 6
^aDay 28

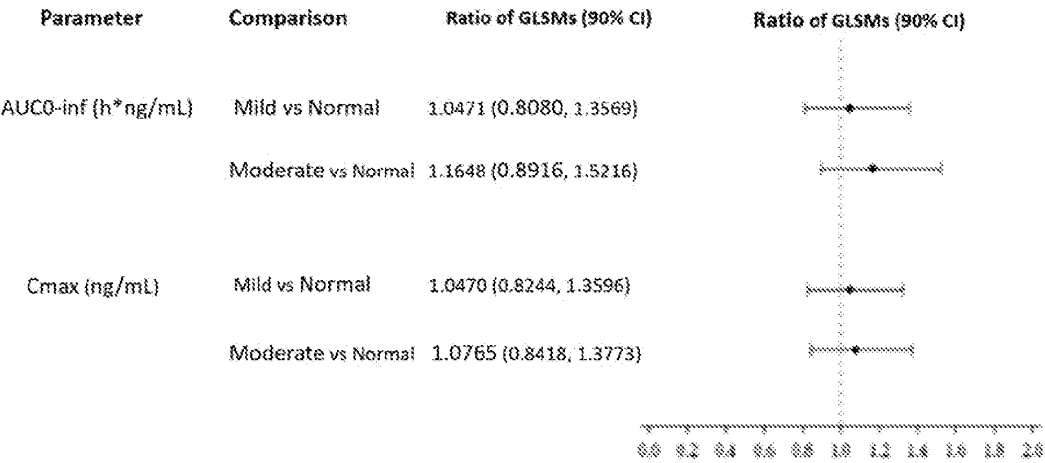
FIG. 10

Table 2-10 Summary statistics of arimoclomol exposure variables stratified by body weight band

Exposure variable	Statistic	8 to 15 kg	15 to 22 kg	22 to 38 kg	38 to 55 kg	>55 kg	All patients
	N	4	5	6	12	7	34
AUC _{0-8h,ss} (h·ng/mL)	Minimum	1660.9	1800.1	1680.9	2143.6	2111.0	1660.9
	Maximum	2048.2	2529.9	3410.8	4815.3	5113.7	5113.7
	Median	1822.3	2099.3	2841.5	3129.4	3382.6	2841.5
	Arithmetic mean	1838.4	2115.3	2689.0	3153.6	3453.1	2825.9
	Arithmetic CV (%)	8.7	13.9	25.4	25.8	25.4	31.0
	Geometric mean	1833.2	2099.2	2608.8	3060.5	3358.6	2701.5
	Geometric CV (%)	8.7	13.8	28.3	25.9	26.1	31.1
C _{max,ss} (ng/mL)	Minimum	303.8	315.6	290.7	372.7	378.1	290.7
	Maximum	386.7	425.2	645.8	840.0	1073.3	1073.3
	Median	338.4	364.8	513.1	630.5	744.9	513.1
	Arithmetic mean	341.8	371.1	497.0	608.0	734.5	548.3
	Arithmetic CV (%)	12.9	11.3	26.1	26.2	27.7	35.5
	Geometric mean	339.7	369.2	481.0	587.0	707.1	516.0
	Geometric CV (%)	12.9	11.5	29.8	28.2	32.0	36.6
C _{min,ss} (ng/mL)	Minimum	133.3	115.4	139.1	160.3	168.0	115.4
	Maximum	163.1	220.3	264.4	403.5	348.1	403.5
	Median	147.1	174.6	227.9	226.2	207.4	205.1
	Arithmetic mean	147.7	177.3	210.9	235.5	225.3	210.2
	Arithmetic CV (%)	9.6	23.9	26.7	31.8	26.9	30.7
	Geometric mean	147.2	172.9	204.0	225.7	219.3	201.5
	Geometric CV (%)	9.6	26.4	29.5	30.6	24.6	29.6

Table 2-10 shows the summary statistics of arimoclomol exposure (AUC_{0-8h,ss}, C_{min,ss} and C_{max,ss}) in CT-ORZY-NPC-002 for all patients and stratified by each of the 5 five weight bands.

Figure 3-6 Impact on Hepatic Impairment in the Single-dose
 Pharmacokinetics of arimoclomol – Trials OR-ARI-HEP-01



CI = confidence interval; GLSM = geometric least squares mean
Source: [OR-ARI-HEP-01, Table 14.2.1-3]

FIG. 12

Table 6-6 Intrinsic Factor Pharmacokinetic Trials

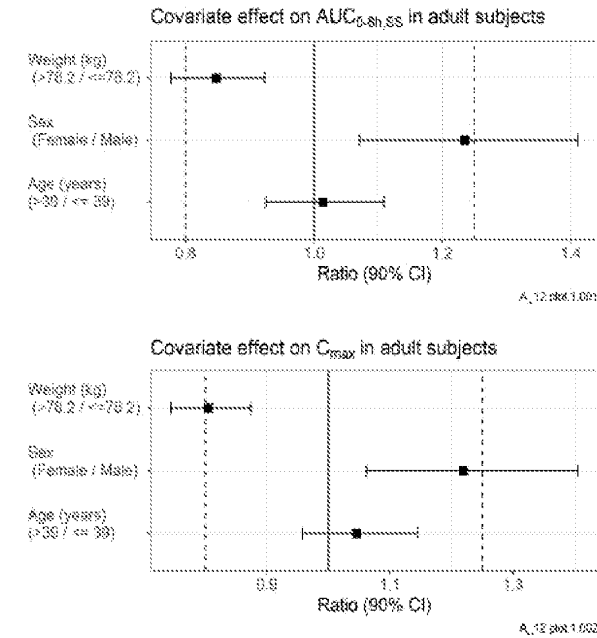
Trial	Ari Dose	Analyte / Matrix	N	Day	AUC ₀₋₈ (ng·h/mL)	AUC ₀₋₂₄ ^a (ng·h/mL)	C _{max} (ng/mL)	t _{max} (h)	t _{1/2} (h)	CL/F (L/h)
OR- ARI- HEP- 01	248 mg SD, Mild hepatic	An / Plasma	8	1	5774 (27.2)	7939 (31.0)	1420 (32.9)	1.0 (0.5,2.0)	4.75 (2.1, 1)	31.3 (31.0)
	248 mg SD, Moderate hepatic	An / Plasma	8	1	5533 (21.2)	8683 (18.3)	1346 (25.5)	2.0 (0.5,6.0 2)	4.92 (18, 7)	28.5 (18.3)
	248 mg SD, Normal hepatic	An / Plasma	8	1	5477 (29.1)	7505 (35.5)	1290 (30.2)	1.25 (1.0,2.5)	4.44 (18, 0)	33.1 (35.5)
	248 mg SD, Mild hepatic	M2 / Plasma	8	1	3730 (31.8)	7640 (44.7)	665 (31.4)	4.0 (3.0,6.0 5)	6.22 (30.7 3)	-
	248 mg SD, Moderate hepatic	M2 / Plasma	8	1	3150 (65.1)	9350 (52.3)	673 (42.0)	6.0 (4.0,8.0)	8.75 (57.9 3)	-
	248 mg SD, Normal hepatic	M2 / Plasma	8	1	3280 (21.2)	6920 (30.8)	618 (20.0)	5.0 (4.0,8.0)	6.33 (35.3 3)	-

Trial	Ari Dose	Analyte / Matrix	N	Day	AUC ₀₋₈ (ng·h/mL)	AUC ₀₋₂₄ ^a (ng·h/mL)	C _{max} (ng/mL)	t _{max} (h)	t _{1/2} (h)	CL/F (L/h)
	248 mg SD, Mild hepatic	M105 / Plasma	8	1	67.7 (198)	1330 (111)	48.7 (79.6)	24.00 (11.97, 24.13)	NC	
	248 mg SD, Moderate hepatic	M105 / Plasma	8	1	NC	475 (160)	21.6 (81.2)	24.00 (4.00, 24.08)	NC	
	248 mg SD, Normal hepatic	M105 / Plasma	8	1	133 (101)	2830 (33.6)	90.7 (38.3)	24.00 (24.00, 24.03)	NC	
OR- ARI- REN- 01 Ongoing results pending §	248 mg SD, Mild renal	An / Plasma	8	1						
	248 mg SD, Moderate renal	An / Plasma	8	1						
	248 mg SD, normal renal	An / Plasma	8	1						

^a For M105 AUC₀₋₂₄,
AUC₀₋₂₄=area under the plasma concentration-time curve from zero to infinity, AUC₀₋₈=area under the plasma concentration-time curve from zero to eight hours postdose, CL/F=oral clearance, C_{max}=maximum observed plasma concentration, t_{1/2}=apparent elimination half-life, t_{max}=time to maximum observed concentration, V_d/F=apparent volume of distribution.
Note: Geometric mean and geometric %CV are presented for all parameters except for t_{max}, for which median and minimum, maximum is presented.
Note: All mean AUC and C_{max} values are multiplied with 0.630241 for conversion to arimoclomol base.

FIG. 13

Figure 3-4 Impact of Age, Sex, and Weight on the Multiple Dose Pharmacokinetics of Arimoclamsol - Population Pharmacokinetic Analysis in Adults, C_{max} (top) AUC₀₋₂₄ (bottom)



Source: [popPK report, Figure I-3 and I-2].
Filled squares indicate calculated ratio (alternative/reference) of geometric means of AUC_{0-24,SS} (upper figure) and C_{max} (lower figure) with 90% CI displayed as error bars.

FIG. 14

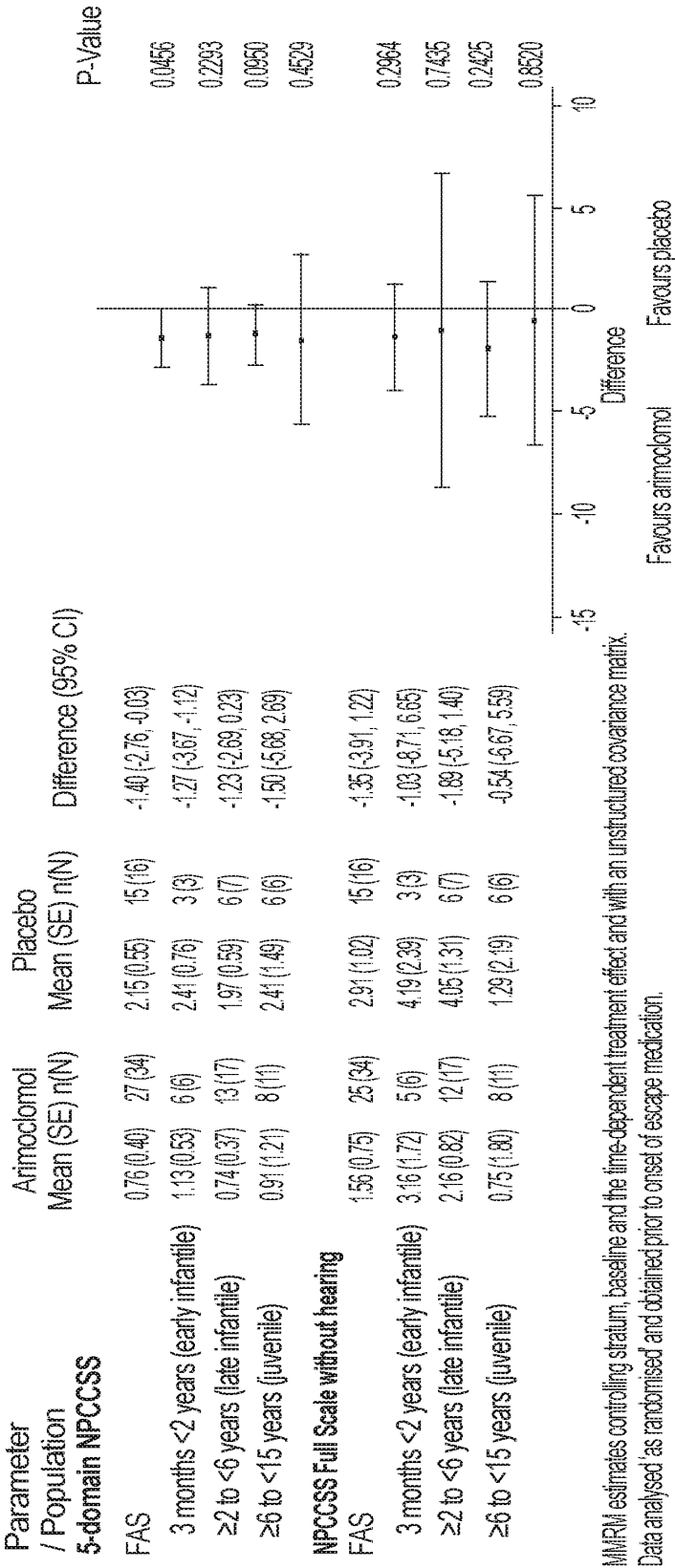
Table 2-5 **Analysis of change from baseline to Month 12 in 5-domain NPCCSS in full population and subgroup with use of miglustat at baseline (FAS)**

	Arimoclonol	Placebo	Arimoclonol versus placebo LS means difference (95% CI)	p-value
Full population	27	15	-1.40 (-2.76; -0.03)	0.0456
Subgroup with use of miglustat at baseline	22	12	-2.06 (-3.49; -0.63)	0.0060

CI = confidence interval; FAS = full analysis set; N = number of patients in FAS; n = number of patients included in the analysis; NPCCSS = NPC Clinical Severity Scale

Source: Figure 2-6 and Figure 2-7.

FIG. 16



P:\Integration_NPC\Exploratory\Programs\MAA120\programs\Q128_129_02_f_forest.png
P:\Integration_NPC\Exploratory\Programs\MAA120\programstrun_all_for_SharePoint.sas

FIG. 17