Primary efficacy assessment - $HbA1_c$ measured 12 months after randomisation

$HbA1_c$ measured 12 months after randomisation – ITT

Table 6.6-1: HbA1c measured 12 months after randomisation – Completeness of data (ITT)

Analysis status	Reason	CSII	MDI	Total
Included	Included	143 (99.3%)	142 (95.3%)	285 (97.3%)
Excluded	No local reason=(home visit); No central reason=(Quantity not sufficient)	0 (0%)	1 (0.7%)	1 (0.3%)
	No local reason=(home visit, see below); No central reason=(no sample received at labs)	0 (0%)	1 (0.7%)	1 (0.3%)
	WD from study prior to 12 months	1 (0.7%)	5 (3.4%)	6 (2%)

Table 6.6-2: HbA1c measured 12 months after randomisation – Lab value used for analysis (ITT)

Age strata	Lab value used for PO analysis (ITT)	CSII	MDI
<5 years	Central	22 (66.7%)	26 (83.9%)
	Local	11 (33.3%)	5 (16.1%)
5-11 years	Central	58 (82.9%)	58 (80.6%)
	Local	12 (17.1%)	14 (19.4%)
12+ years	Central	32 (80%)	33 (84.6%)
	Local	8 (20%)	6 (15.4%)
Total	**Central**	**112 (77.8%)**	**117 (78.5%)**
	Local	**31 (21.5%)**	**25 (16.8%)**

Table 6.6-3: HbA1c measured 12 months after randomisation – Results (ITT)

Age-group	HbA1c (mmol/mol) at 12 months	CSII	MDI	Total	Least Squares Mean CSII (95% CI)	Least Squares Mean MDI (95% CI)	Least Squares Mean Difference between treatment groups (CSII-MDI) across all age-groups (95% CI)	P-value
7mths - < 5yrs	Missing	0	0	0	60.9 (58.5,63.3)	58.5 (56.1,60.9)	2.4 (-0.4, 5.3)	0.09
	N	33	31	64				
	Mean (SD)	63.9 (12.1)	58.4 (9.9)	61.2 (11.3)				
	Median (IQR)	63.6 (56, 71)	58 (51, 65)	62.5 (54, 69)				
	(Min, Max)	(40, 88)	(36, 83)	(36, 88)				
5yrs - <12yrs	Missing	0	0	0				
	N	70	72	142				
	Mean (SD)	58 (11.4)	59.3 (11.4)	58.7 (11.4)				
	Median (IQR)	57 (50, 65)	58 (49, 65)	57 (50, 65)				
	(Min, Max)	(33, 92)	(43, 89)	(33, 92)				
12yrs - <16yrs	Missing	0	0	0				
	N	40	39	79				
	Mean (SD)	61.3 (13.3)	54.7 (14.7)	58.1 (14.3)				
	Median (IQR)	63.5 (50.5, 69.5)	51 (45, 66)	58 (45, 68)				
	(Min, Max)	(35, 84)	(31, 94)	(31, 94)				
Overall	**Missing**	**0**	**0**	**0**				
	N	**143**	**142**	**285**				
	Mean (SD)	**60.3 (12.3)**	**57.9 (12.2)**	**59.1 (12.3)**				
	Median (IQR)	**60 (52, 68)**	**57 (48, 65)**	**58 (50, 67)**				
	(Min, Max)	**(33, 92)**	**(31, 94)**	**(31, 94)**				

Note: Lower mmol/mol indicates better glycaemic control.

Figure 6.6-1: Primary outcome results Meta-Analysis and Forest plot across sites (ITT)

Study or Subgroup	CSIII Mean	CSIII SD	CSIII Total	MDI Mean	MDI SD	MDI Total	Weight	Mean Difference IV, Fixed, 95% CI
00036 Norfolk and Norwich University Hospitals NHS	60.7555	11.9268604	4	49.25	8.0156098	4	3.7%	11.51 [-2.58, 25.59]
00086 Doncaster Royal Infirmary	55.25	10.9642275	8	59.6666667	11.6404467	9	6.3%	-4.42 [-15.17, 6.33]
00104 Stafford Hospital	0	0	0	57	4.2426407	2		Not estimable
00114 Southampton University Hospitals NHS Trust	64.2142857	15.5324899	14	61.1333333	13.0376743	15	6.6%	3.08 [-7.39, 13.56]
00133 Birmingham Childrens Hospital	61.5	13.541183	12	59.5555556	11.7910041	9	6.2%	1.94 [-8.92, 12.81]
00148 Ipswich Hospital	56.6666667	8.3864971	3	48.3333333	4.7258156	3	6.1%	8.33 [-2.56, 19.23]
00160 Royal Preston Hospital	0	0	0	67.5	7.7781746	2		Not estimable
00213 Nottingham University Hospital NHS Trust	57.7741935	11.1376529	31	55.8666667	13.6879845	30	18.5%	1.91 [-4.37, 8.18]
00243 Alder Hey Childrens NHS Foundation Trust	58.6923077	11.3517196	26	55.1666667	12.7370281	24	16.2%	3.53 [-3.18, 10.23]
00248 Sheffield Childrens NHS Foundation Trust	64	13.2916014	4	52.6666667	10.7857931	3	2.3%	11.33 [-6.52, 29.18]
00326 East Surrey Hospital	61.2	4.5077711	3	69.25	10.8435849	4	5.2%	-8.05 [-19.84, 3.74]
01527 Royal Blackburn Hospital	61.07983	12.6936387	5	61.6666667	11.2368442	6	3.6%	-0.59 [-14.89, 13.72]
04913 Cardiff and Vale University Local Health Boa	59.3333333	9.8361578	9	61.5555556	9.0015431	9	9.6%	-2.22 [-10.93, 6.49]
05042 Oxford Radcliffe Hospitals NHS Trust	62.3333333	15.8336945	18	54.7647059	10.9231944	17	9.0%	7.57 [-1.40, 16.54]
12617 The Newcastle Upon Tyne Hospitals NHS	68.3333333	8.2623645	6	68.8	9.2032603	5	6.7%	-0.47 [-10.90, 9.96]
Total (95% CI)			**143**			**142**	**100.0%**	**2.16 [-0.54, 4.86]**

Heterogeneity: $Chi^2 = 11.21$, $df = 12$ ($P = 0.51$); $I^2 = 0\%$
Test for overall effect: $Z = 1.57$ ($P = 0.12$)

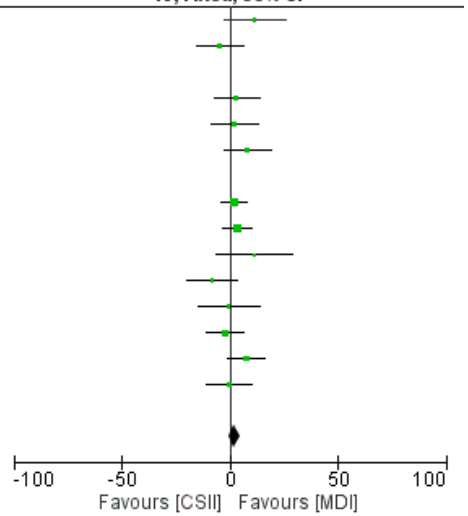


Table 6.6-4: Baseline characteristics of children that were randomised and have a primary outcome measurement (ITT)

	CSII	MDI	Total
Age at randomisation (years)			
Missing	0	0	0
N	143	142	285
Mean (SD)	9.1 (4.1)	9 (4.2)	9 (4.1)
Median (IQR)	9.9 (5.6, 12.3)	9.3 (5.7, 12.5)	9.7 (5.7, 12.3)
(Min, Max)	(0.8, 16)	(0.7, 15.4)	(0.7, 16)
Age cat (strata cat)			
Missing	0	0	0
N	143	142	285
7mths – <5 yrs	33 (23.1%)	31 (21.8%)	64 (22.5%)
5 – <12 yrs	70 (49%)	72 (50.7%)	142 (49.8%)
12-15 yrs	40 (28%)	39 (27.5%)	79 (27.7%)
Age cat (EudraCT)			
Missing	0	0	0
N	143	142	285
Infants and toddlers	8 (5.6%)	6 (4.2%)	14 (4.9%)
Children	95 (66.4%)	97 (68.3%)	192 (67.4%)
Adolescents	40 (28%)	39 (27.5%)	79 (27.7%)
Gender			
Missing	0	0	0
N	143	142	285
Female	71 (49.7%)	64 (45.1%)	135 (47.4%)
Male	72 (50.3%)	78 (54.9%)	150 (52.6%)
Ethnicity			
Missing	1	3	4
N	142	139	281
Asian or Asian British	3 (2.1%)	3 (2.2%)	6 (2.1%)
Black or British Black	0 (0%)	3 (2.2%)	3 (1.1%)
British White	124 (87.3%)	112 (80.6%)	236 (84%)
Indian	2 (1.4%)	2 (1.4%)	4 (1.4%)
Mixed	4 (2.8%)	6 (4.3%)	10 (3.6%)
Not stated	0 (0%)	0 (0%)	3 (1.1%)
Other	2 (1.4%)	2 (1.4%)	4 (1.4%)
Other White	6 (4.2%)	7 (5%)	13 (4.6%)
Pakistani	1 (0.7%)	4 (2.9%)	5 (1.8%)
Deprivation score (continuous)			
Missing	7	6	13
N	136	136	272
Mean (SD)	25 (19.4)	20.9 (17)	22.9 (18.3)
Median (IQR)	19.3 (8.9, 38.5)	13.9 (7.7, 29.5)	16.7 (8.3, 35)
(Min, Max)	(1.8, 77.1)	(1.6, 73.9)	(1.6, 77.1)

	CSII	MDI	Total
Deprivation score (quintile categories)			
Missing	7	6	13
N	136	136	272
1 (<=8.49)	32 (23.5%)	39 (28.7%)	71 (26.1%)
2 (8.5 – 13.79)	23 (16.9%)	29 (21.3%)	52 (19.1%)
3 (13.8 – 21.35)	18 (13.2%)	22 (16.2%)	40 (14.7%)
4 (21.36 – 34.17)	24 (17.6%)	16 (11.8%)	40 (14.7%)
5 (>=34.18)	39 (28.7%)	30 (22.1%)	69 (25.4%)

Figure 6.6-2: HbA1c mmol/mol – Mean profile plots (<5 years old) (ITT)

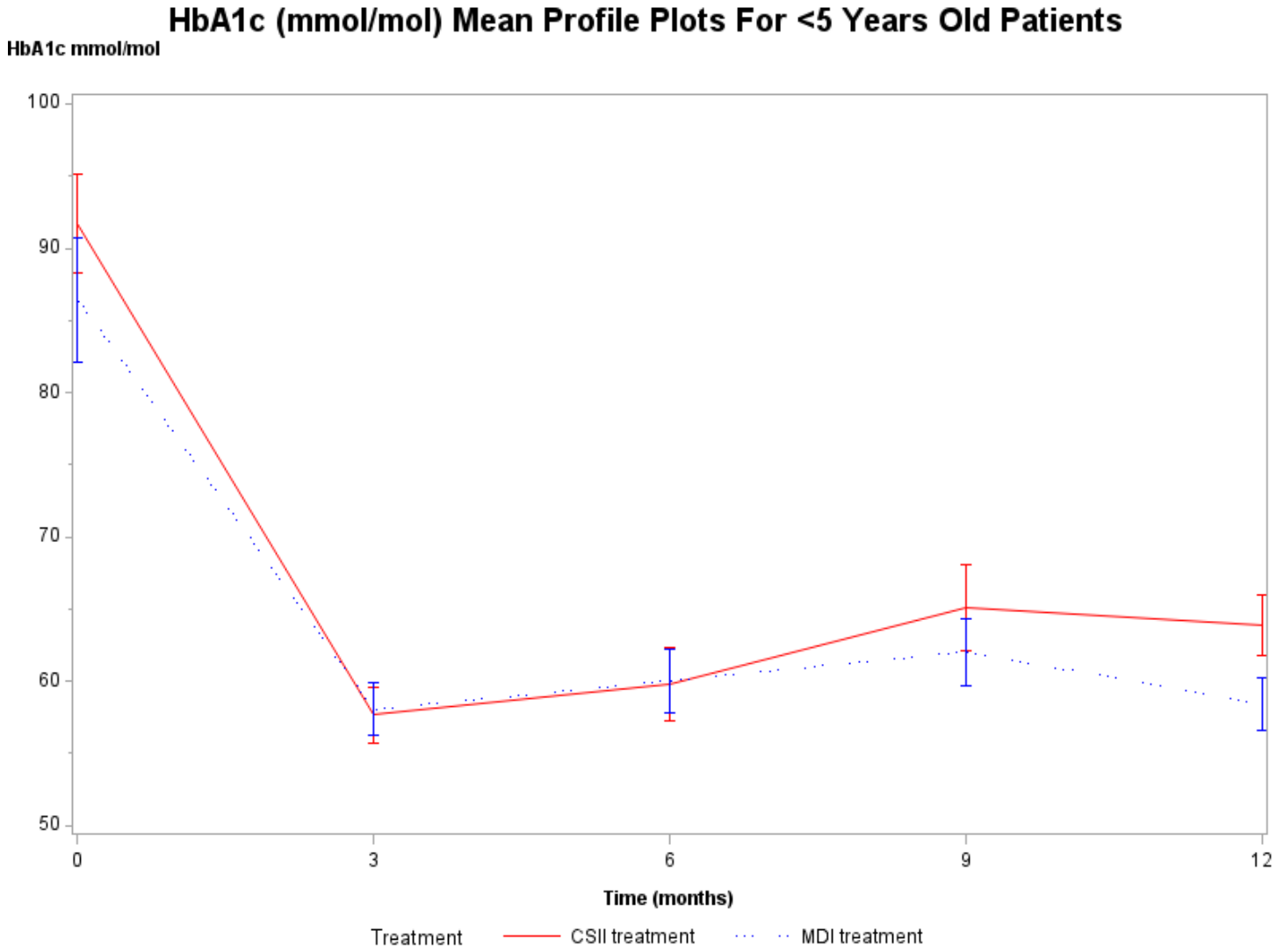


Figure 6.6-3: HbA1c mmol/mol – Mean profile plots (5-11 years old) (ITT)

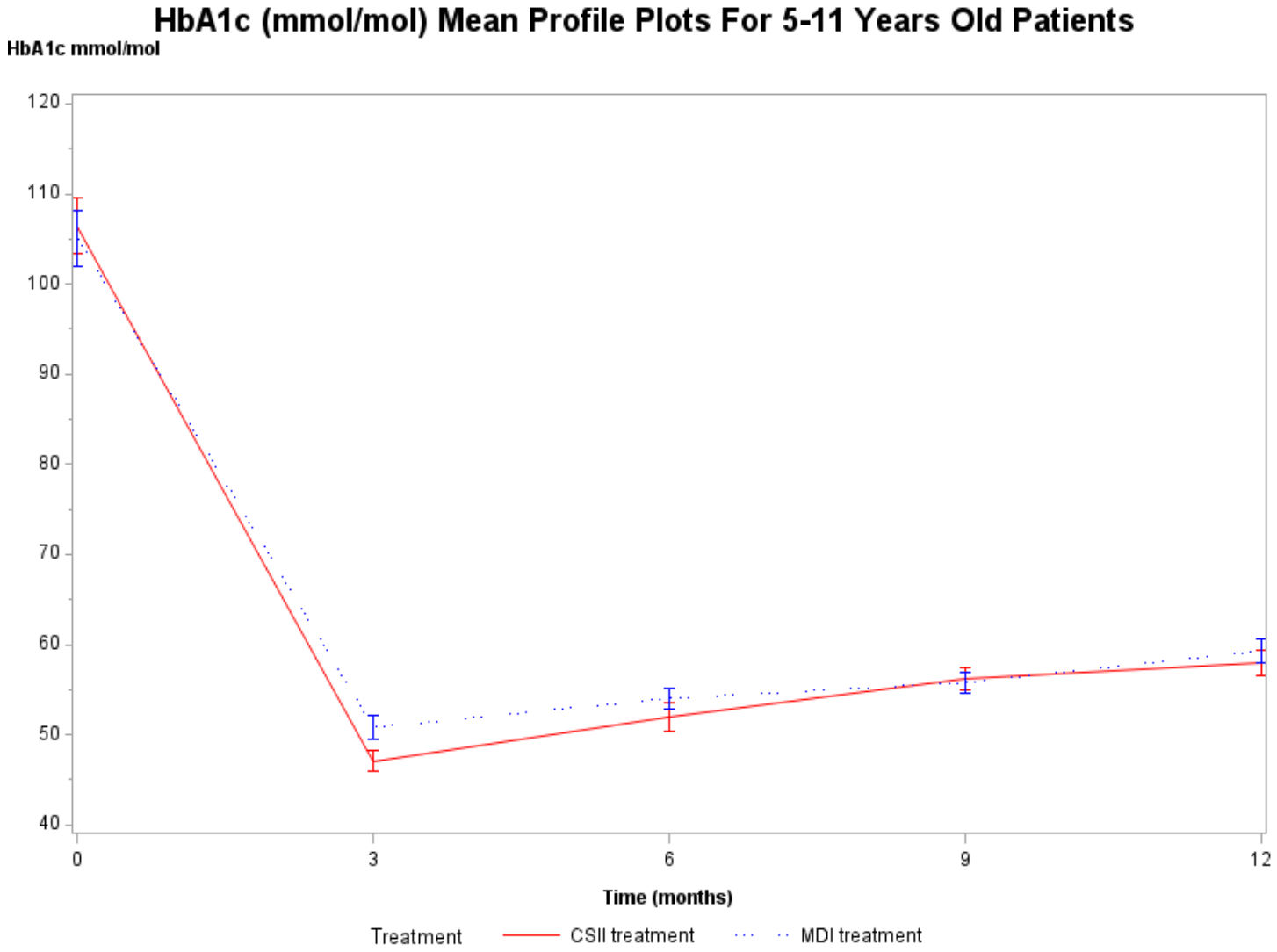
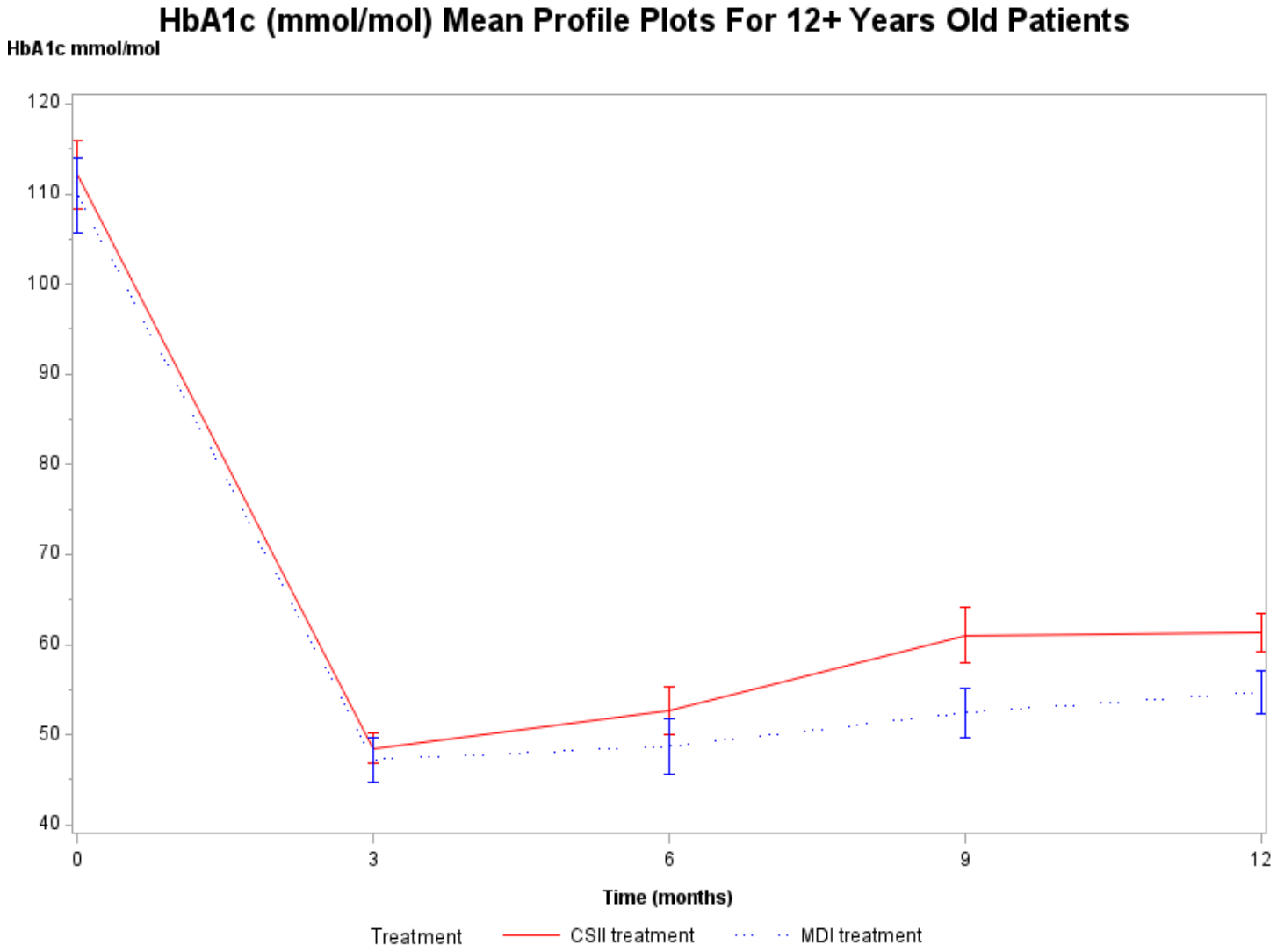


Figure 6.6-4: HbA1c mmol/mol – Mean profile plots (12+ years old) (ITT)



HbA1c measured 12 months after randomisation – Per-protocol

Table 6.6-5: HbA1c measured 12 months after randomisation – Completeness of data (Per-protocol)

Analysis status	Reason	CSII	MDI	Total
Included	Included	87 (60.4%)	66 (44.3%)	153 (52.2%)
Excluded	At least one major PD	56 (38.9%)	76 (51%)	132 (45.1%)
	At least one major PD and were also excluded from ITT analysis: (WD from study prior to 12 months)	1 (0.7%)	1 (0.7%)	2 (0.7%)
	Excluded from ITT analysis: (No local reason=(home visit); No central reason=(Quantity not sufficient))	0 (0%)	1 (0.7%)	1 (0.3%)
	Excluded from ITT analysis: (No local reason=(home visit, see below); No central reason=(no sample received at labs))	0 (0%)	1 (0.7%)	1 (0.3%)
	Excluded from ITT analysis: (WD from study prior to 12 months)	0 (0%)	4 (2.7%)	4 (1.4%)

Table 6.6-6: HbA1c measured 12 months after randomisation – Lab value used for analysis (Per-protocol)

Age strata	Lab value used for PO analysis (per-protocol)	CSII	MDI
<5 years	Central	15 (65.2%)	11 (100%)
	Local	8 (34.8%)	-
5-11 years	Central	34 (82.9%)	27 (84.4%)
	Local	7 (17.1%)	5 (15.6%)
12+ years	Central	18 (78.3%)	20 (87%)
	Local	5 (21.7%)	3 (13%)
Total	**Central**	**67 (77.0%)**	**58 (87.9%)**
	Local	**20 (23.0%)**	**8 (12.1%)**

Table 6.6-7: HbA1c measured 12 months after randomisation – Results (Per-protocol)

Age-group	HbA1c at 12 months	CSII	MDI	Total	Least Squares Mean CSII (95% CI)	Least Squares Mean MDI (95% CI)	Least Squares Mean Difference between treatment groups (CSII-MDI) across all age-groups (95% CI)	P-value
7mths - < 5yrs	Missing	0	0	0	60.2 (56.4,63.9)	59.3 (55.3,63.3)	0.9 (-3.2, 5)	0.67
	N	23	11	34				
	Mean (SD)	62.6 (13.1)	56.2 (11)	60.5 (12.6)				
	Median (IQR)	63 (54, 71)	56 (48, 68)	60.5 (52, 70)				
	(Min, Max)	(40, 88)	(36, 70)	(36, 88)				
5yrs - <12yrs	Missing	0	0	0				
	N	41	32	73				
	Mean (SD)	57.9 (11.8)	59.7 (10.8)	58.7 (11.3)				
	Median (IQR)	57 (50, 63)	61 (50.5, 65)	58 (50, 65)				
	(Min, Max)	(33, 90)	(43, 83)	(33, 90)				
12yrs - <16yrs	Missing	0	0	0				
	N	23	23	46				
	Mean (SD)	57.6 (14.2)	57.8 (16.8)	57.7 (15.4)				
	Median (IQR)	58 (43, 67)	57 (45, 73)	57.5 (44, 67)				
	(Min, Max)	(35, 83)	(32, 94)	(32, 94)				
Overall	**Missing**	**0**	**0**	**0**				
	N	**87**	**66**	**153**				
	Mean (SD)	**59 (12.8)**	**58.4 (13.1)**	**58.8 (12.9)**				
	Median (IQR)	**58 (50, 67)**	**57.5 (47, 67)**	**58 (48, 67)**				
	(Min, Max)	**(33, 90)**	**(32, 94)**	**(32, 94)**				

Note: Lower mmol/mol indicates better glycaemic control.

Table 6.6-8: Baseline characteristics of children that were randomised and have a primary outcome measurement (Per-protocol)

	CSII	MDI	Total
Age at randomisation (years)			
Missing	0	0	0
N	87	66	153
Mean (SD)	8.6 (4.2)	9.7 (4.2)	9.1 (4.2)
Median (IQR)	9.1 (4.7, 12.2)	10.1 (7.1, 13.7)	9.3 (5.7, 12.5)
(Min, Max)	(0.8, 16)	(0.9, 15.3)	(0.8, 16)
Age cat (strata cat)			
Missing	0	0	0
N	87	66	153
7mths – <5 yrs	23 (26.4%)	11 (16.7%)	34 (22.2%)
5 – <12 yrs	41 (47.1%)	32 (48.5%)	73 (47.7%)
12-15 yrs	23 (26.4%)	23 (34.8%)	46 (30.1%)
Age cat (EudraCT)			
Missing	0	0	0
N	87	66	153
Infants and toddlers	6 (6.9%)	3 (4.5%)	9 (5.9%)
Children	58 (66.7%)	40 (60.6%)	98 (64.1%)
Adolescents	23 (26.4%)	23 (34.8%)	46 (30.1%)
Gender			
Missing	0	0	0
N	87	66	153
Female	44 (50.6%)	29 (43.9%)	73 (47.7%)
Male	43 (49.4%)	37 (56.1%)	80 (52.3%)
Ethnicity			
Missing	1	1	2
N	86	65	151
Asian or Asian British	0 (0%)	2 (3.1%)	2 (1.3%)
Black or British Black	0 (0%)	3 (4.6%)	3 (2%)
British White	78 (90.7%)	51 (78.5%)	129 (85.4%)
Indian	2 (2.3%)	1 (1.5%)	3 (2%)
Mixed	3 (3.5%)	5 (7.7%)	8 (5.3%)
Not stated	0 (0%)	0 (0%)	1 (0.7%)
Other	0 (0%)	2 (3.1%)	2 (1.3%)
Other White	2 (2.3%)	1 (1.5%)	3 (2%)
Pakistani	1 (1.2%)	0 (0%)	1 (0.7%)
Deprivation score (continuous)			
Missing	5	4	9
N	82	62	144
Mean (SD)	21.7 (18.9)	21 (16.8)	21.4 (18)
Median (IQR)	13.7 (8.4, 31.8)	15.1 (8.4, 30.9)	14.4 (8.4, 31.4)
(Min, Max)	(2.1, 67.9)	(1.6, 73.9)	(1.6, 73.9)

	CSII	MDI	Total
Deprivation score (quintile categories)			
Missing	5	4	9
N	82	62	144
1 (<=8.49)	22 (26.8%)	16 (25.8%)	38 (26.4%)
2 (8.5 – 13.79)	19 (23.2%)	14 (22.6%)	33 (22.9%)
3 (13.8 – 21.35)	12 (14.6%)	11 (17.7%)	23 (16%)
4 (21.36 – 34.17)	10 (12.2%)	7 (11.3%)	17 (11.8%)
5 (>=34.18)	19 (23.2%)	14 (22.6%)	33 (22.9%)

Table 6.6-9: HbA1c measured 12 months after randomisation – Measurement of local lab HbA1c at 12 months

Age strata	Local lab HbA1c reason (Verbatim)	CSII	MDI
<5 years	HbA1c measured	33 (100%)	31 (96.9%)
5-11 years	HbA1c measured	69 (97.2%)	70 (92.1%)
	additional visit Hba1c analyser not available	-	1 (1.3%)
	home visit	-	1 (1.3%)
	no clinic runnning was unable to undertake HbA1c locally as DCA advantage was not available	1 (1.4%)	-
12+ years	HbA1c measured	39 (97.5%)	36 (87.8%)
	No reason provided	-	1 (2.4%)
	insufficient sample	-	1 (2.4%)
	non clinic visit	1 (2.5%)	-
	not a routine clinic visit HbA1c analyser unavailable	-	1 (2.4%)
Total	HbA1c measured	141 (97.9%)	137 (91.9%)
	No reason provided	-	1 (0.7%)
	additional visit Hba1c analyser not available	-	1 (0.7%)
	home visit	-	1 (0.7%)
	insufficient sample	-	1 (0.7%)
	no clinic runnning was unable to undertake HbA1c locally as DCA advantage was not available	1 (0.7%)	-
	non clinic visit	1 (0.7%)	-
	not a routine clinic visit HbA1c analyser unavailable	-	1 (0.7%)

Table 6.6-10: HbA1c measured 12 months after randomisation – Measurement of central lab HbA1c at 12 months

Age strata	Central lab HbA1c reason (Verbatim)	CSII	MDI
<5 years	HbA1c measured	23 (69.7%)	26 (81.3%)
	Quantity not sufficient	5 (15.2%)	4 (12.5%)
	no record of log at site	1 (3%)	-
	no sample recieved at labs	-	1 (3.1%)
	participant did not wish to do this	1 (3%)	-
	prior to Version 4 of protocol being received at site	2 (6.1%)	-
	sample not taken unable to obtain blood 2 attempts made on 2 separate days	1 (3%)	-
5-11 years	HbA1c measured	59 (83.1%)	59 (77.6%)
	None returned from lab	1 (1.4%)	-
	Quantity not sufficient	5 (7%)	8 (10.5%)
	Test not performed	-	1 (1.3%)
	bloods not taken	1 (1.4%)	-
	no sample record	-	1 (1.3%)
	no staff available- home visit	1 (1.4%)	-
	prior to Version 4 of protocol being received at site	3 (4.2%)	3 (3.9%)
12+ years	HbA1c measured	32 (80%)	33 (80.5%)
	DNA'd appointment only minimal data available	-	1 (2.4%)
	DNA'd multiple appointments	-	1 (2.4%)
	Quantity not sufficient	4 (10%)	3 (7.3%)
	prior to Version 4 of protocol being received at site	4 (10%)	1 (2.4%)
Total	HbA1c measured	114 (79.2%)	118 (79.2%)
	None returned from lab	1 (0.7%)	-
	Quantity not sufficient	14 (9.7%)	15 (10.1%)
	Test not performed	-	1 (0.7%)
	bloods not taken	1 (0.7%)	2 (1.4%)
	no record of log at site	1 (0.7%)	-
	no sample recieved at labs	-	1 (0.7%)
	no sample record	-	1 (0.7%)
	no staff available- home visit	1 (0.7%)	-
	participant did not wish to do this	1 (0.7%)	-
	prior to Version 4 of protocol being received at site	9 (6.3%)	4 (2.7%)
	sample not taken unable to obtain blood 2 attempts made on 2 separate days	1 (0.7%)	-

Additional analyses

Table 6.7-4: Additional Analyses – Primary efficacy assessment – HbA1c measured 12 months after randomisation (ITT)

Analysis	Least-Square Mean Difference between treatment groups (CSII-MDI) across all age-groups (95% CI)	P-value
Primary outcome ITT analysis	*2.4 (-0.5, 5.2)*	*0.10*
Total related AEs as a covariate	2.5 (-0.4, 5.3)	0.09
Deprivation score (quintile) as a covariate	2.2 (-0.7, 5)	0.14
Deprivation score (continuous) as a covariate	2.2 (-0.7, 5)	0.14
Abnormal coeliac screen result as a covariate	1.7 (-1.7, 5.1)	0.33