SUPPLEMENTARY METHODS

Experimental treatment

LT4+LT3 group

The LT4 tablet dosage, used before enrolment, was reduced. The reduced LT4 rate was replaced with a customized LT3 dose, calculated based on the total dose of LT4 at baseline, to maintain the T4/T3 ratio between 13:1 and 20:1, in line with the 2012 guidelines of the European Thyroid Association (ETA) (1). Considering that the intestinal absorption of LT4 is equal to 80% and that the physiological ratio T4/T3 is 16:1, being "x" the dose of LT4 in µg able to normalize TSH during previous LT4 monotherapy, the dose of LT3 in µg (y) required is 0.8x:17. The dose of LT4 in µg to be continued is equal to 16y, multiplied by 1.25, a correction factor that considers that the absorption of LT4 is 80% while that of T3 is 100%.

The daily LT3 dosage was then divided into two doses, the greater of which was to be taken in the evening, following the molecule's half-life and its physiological nocturnal peak, as well as with international guidelines (1). Therefore, subjects enrolled in the LT4+LT3 group took a reduced dose of LT4 (in tablets) and 1/3 of the dose of LT3 (in drops) in the morning, fasting at least 30 minutes before breakfast, and 2/3 of the dose of LT3 (in drops) in the evening, before going to bed, at least two hours after the last meal of the day.

LT4+placebo group

Subjects randomized in the LT4+placebo group continued the LT4 dosage at enrolment, dividing it into two administrations. The ongoing dosage of LT4 had been reduced by approximately 20% and replaced with an equal dose of LT4 in drops, with the sole purpose of reproducing the modality designed for the LT4+LT3 group and maintaining double blindness. In this way, patients took 80% of the initial dose in tablets and the remaining 20% in drops, both in the morning, and fasting at least 30 minutes before breakfast. In the evening, patients took a dose of placebo (in drops), before going to bed. As described above for the LT4+LT3 group, drug bottles were prepared by the

randomizing clinician in boxes and bottles identical and indistinguishable from those of the LT4+LT3 group and then provided by the investigators during the foreseen protocol visits.

Questionnaires

The ThyPRO questionnaire is a thyroid-specific questionnaire consisting of 85 questions grouped in 13 multi-item scales. The 13 domains concern hypo- and hyperthyroid symptoms, goitre symptoms, eye symptoms, tiredness, cognitive problems, anxiety, depression, emotional susceptibility, impaired social life, impaired daily life, impaired sex-life, cosmetic complaints, and item 12. Considering that the latter scale refers to the overall impact of thyroid disease, from here on it will be called "overall impact". Each item is rated on a 5-point scale from 0 (not at all) to 4 (very much), referring to the last 4 weeks. Each of the 13 ThyPRO scales is evaluated as a summary score and transformed linearly to a range of 0–100, with higher scores indicating more thyroid-related complaints. Consequently, for each domain, higher scores mean worse symptoms and a higher score for item 12 means a greater impact of thyroid disease on QoL.

Morisky Medication Adherence Scale is a self-reported scale, consisting of 8 items: 4 items regard common medication-taking behaviours leading to the omission of drug, and the other 4 items address the circumstances surrounding adherence behaviour. The first 7 items are yes/no questions and can score 1 or 0; the last item is a 5-point scale rating from 0 to 4. The total score is given by the sum of the score of the first 7 items plus the score of the last item divided by four. A score lower than 6 indicates poor adherence to therapy.

After the end of the study, a telephone questionnaire was conducted with predefined multiple-choice questions to investigate the preference for experimental therapy and any difficulties with the new therapeutic scheme. Below are the questions used and the possible answers:

1) Comparing the therapy taken in the 6 months of the study and the therapy you previously took, which one did you prefer?

A) Previous therapy. If previous therapy, why?

A1) I felt worse physically

A2) I felt worse mentally

A3) I felt worse physically and mentally

B) Experimental therapy. If experimental therapy, why?

B1) I felt better physically

B2) I felt better mentally

B3) I felt better physically and mentally

C) No preference

2) Did you find experimental therapy more uncomfortable?

A) Yes. If yes, why (more choices possible)?

A1) More complex therapeutic scheme

A2) Counting drops

A3) Twice-daily administration

A4) Side effects

A5) Too many medical checks

B) No

Genotyping

DNA was extracted from blood samples (200 µl) using the QIAamp DNA Blood Kit and quantified with NanoDrop™ 2000 spectrophotometer (ThermoFisher Scientific, Waltham, MA, USA).

DIO2 genotyping was performed by Sanger sequencing. PCR amplification of the *DIO2* region containing the rs225014 SNP was carried out using the following primer pairs: forward 5'-TGCTCTGAAGGAAATACCACACT-3' and reverse 5'-CAGGAAGTCAGCCACTGAGG-3'. PCR products were sequenced by the BigDye Terminator v3.1 Cycle Sequencing Kit (Life Technologies, Carlsbad, CA, United States), according to the following conditions: pre-denaturation

60 s at 96°C; 30 cycles of denaturation at 96°C for 10 s, primer annealing at 50°C for 5 s and extension at 60°C for 4 min. Sequence products were then analyzed by 3130 Genetic Analyzer (Applied Biosystems, Waltham, MA, USA).

MCT10 polymorphism rs17606253 was analysed in duplicate by CFX96™ Real-Time PCR Detection System (BioRad) using the pre-designed TaqMan SNP genotyping assay (#4351376 Taqman SNP assay MTO; Applied Biosystem), following the manufacturer's instructions. The CFX Manager software was used for discrimination between wild-type (WT), hetero-, and derived homozygous allelic states.

SUPPLEMENTARY RESULTS

Influence of DIO2 and MCT10 SNPs on experimental treatment outcomes

The allele frequencies of *DIO2* rs225014 and *MCT10* rs17606253 are shown in supplementary table 4. No deviation from the Hardy-Weinberg equilibrium was observed ($p>0.05$).

Considering a recessive genetic model (supplementary table 5), subjects homozygous for *DIO2* rs225014 had higher scores for the overall impact of the thyroid disease (item12 of the ThyPRO questionnaire) and cognitive problems compared to WT (43.18±29.77 vs 19.53±20.80, $p=0.05$ and 39.39±28.34 vs 19.10±17.54, $p=0.04$), at V0 during LT4 monotherapy. At the end of the combination treatment, these differences disappeared in the LT4+LT3 group. No *DIO2* genotype-related differences were found at V0 for pituitary-thyroid axis compensation or tissue markers of peripheral thyroid hormone action. At V3, WT had significantly higher TSH compared to heterozygous, both in the study ($p=0.04$) and in the LT4+placebo group ($p=0.04$).

With the approach of a recessive model, no differences for any endpoint were found between the genotypes of *MCT10* either at V0 or at V3, probably due to the low number of homozygotes.

Thus, we carried out the subsequent analysis considering a dominant genetic model (supplementary Table 6): subjects carrying at least one mutant allele *versus* all the other subjects. Then, we combined the two SNPs (*DIO2+MCT10* group), including patients harbouring at least one

105 varied allele in each gene. One subject in the LT4+placebo group did not undergo genetic analysis,
106 for the inadequacy of the sample. No differences in allele frequencies were found between the study
107 and LT4+placebo groups ($p>0.05$).

108 At baseline, when subjects both in the study and in the LT4+placebo group were on LT4
109 monotherapy, no differences were found between carriers of the WT and derived allele of single or
110 combined SNPs for the following end-points: pituitary-thyroid axis compensation, reported
111 symptoms of hypothyroidism, QoL and tissue markers of peripheral thyroid hormone action
112 (supplementary table 7). At the end of the study, carriers of the derived *DIO2* allele reported more
113 frequently to be asthenic compared to WT (57% vs 45%, $p=0.02$). However, they did not differ for
114 QoL, thyroid hormones or TSH serum levels, and tissue markers of peripheral thyroid hormone
115 action. No differences were found for the same outcomes between derived *MCT10* or *DIO2+MCT10*
116 carriers compared to WT at the end of the study (supplementary table 8).

117 At the across visit analysis, fT4 decreased and fT3/fT4 increased in all groups ($p<0.001$),
118 while fT3 increased in carriers of the derived *MCT10* and *DIO2 + MCT10* alleles, but not in *DIO2*
119 WT or carriers of *DIO2* derived alleles. The improvement of the impact of thyroid disease on QoL
120 was demonstrated by the significant decrease in Item 12 of the ThyPRO questionnaire in both groups.

121 Finally, we considered only carriers of derived alleles, comparing study and LT4+placebo
122 groups. Considering *DIO2*-rs225014 carriers, subjects treated with combination therapy had higher
123 fT3 ($p<0.001$) and higher ft3/fT4 ($p<0.001$) compared to placebo, at the end of the 6-month treatment.
124 They did not differ for QoL or tissue markers. Considering *MCT10*-rs17606253 carriers, subjects
125 treated with combination therapy had higher fT3 ($p=0.01$), lower fT4 ($p=0.03$) and, higher fT3/fT4
126 ($p=0.01$) compared to placebo, at the end of the 6-month treatment. They did not differ for QoL or
127 tissue markers. Considering the carriers of *DIO2+MCT10*, subjects treated with combination therapy
128 did not differ for thyroid compensation but did have a higher score at item 12 of the ThyPRO
129 questionnaire ($p=0.03$) compared to placebo, at the end of the 6-month treatment.

At linear regression analysis, no genotype was predictive of serum TSH, fT3, and fT4 levels or of the fT3/fT4 ratio. Genotypes did not influence patient preference for LT4+LT3 combination therapy, with most of the patients showing no preference.

SUPPLEMENTAL REFERENCES

1. Wiersinga WM, Duntas L, Fadeyev V, Nygaard B, Vanderpump MP. 2012 ETA Guidelines: The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism. European thyroid journal. 2012;1(2):55-71.

Supplementary table 1. Measured serum parameters at V0, V1, V2, and V3 and the specific methods used for measurement.

	Reference range	**Type of assay method**	**Company**	**CV %**
TSH (mcIU/mL)	0.35-4.94	Chemiluminescent immunoassay	Beckman Coulter Inc, USA	≤10
fT4 (pg/mL)	6-12	Chemiluminescent immunoassay	Beckman Coulter Inc, USA	≤10
fT3 (pg/mL)	2.5-3.9	Chemiluminescent immunoassay	Beckman Coulter Inc, USA	≤12
TPOAb (IU/ml)	<9	Chemiluminescent immunoassay	Beckman Coulter Inc, USA	<12
Total-CH (mg/dL)	<200	Enzymatic colorimetric assay	Beckman Coulter Inc, USA	1
HDL-CH (mg/dL)	>40	Enzymatic colorimetric assay	Beckman Coulter Inc, USA	2
Triglycerides (mg/dL)	<180	Enzymatic colorimetric assay	Beckman Coulter Inc, USA	2
SHBG (nmol/L)	Female 19.8-155.2 Male 13.5-71.4	Chemiluminescent immunoassay Architect	Abbott GmbH & Co, Germany	10
BAP (mcg/L)	0-20.1	Chemiluminescent immunoassay	Beckman Coulter Inc, USA	2
CTX (ng/dL)	11-75	ELISA	Immunodiagnostic Systems Limited, UK	<10
Osteocalcin (ng/mL)	4.6-65.4	Chemiluminescent immunoassay Liaison XL	DiaSorin, Italy	<10

Footnotes: CV: coefficient of variability; TSH: Thyroid Stimulating Hormone; fT4: free-thyroxine; fT3: free-triiodothyronine; TPOAb: antibodies to thyroperoxidase; Total-CH: total cholesterol; HDL-

CH: High-Density Lipoprotein cholesterol; SHBG: Sex Hormone-Binding Globulin; BAP: bone isoenzyme of alkaline phosphatase; CTX: C-terminal telopeptide of type 1 collagen.

166 Supplementary table 2. Doses of prescribed thyroid hormones.

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	LT4+LT3 group	LT4+placebo group	p
Weekly thyroid hormone dose (µg/week)			
V0	784.5 ± 201.7	800.4 ± 240.8	0.67
V1	779.5 ± 202.7	787.9 ± 239.1	0.83
V2	741.5 ± 193.1	777.6 ± 225.5	0.34
V3	710.7 ± 183.2	755.8 ± 219.7	0.22
p	0.10	0.82	
LT4 daily dose (µg/daily)			
V0	110.8 ± 28.7 *	114.3 ± 34.4	0.51
V1	105.0 ± 27.4 *	112.0 ± 34.5	0.20
V2	100.0 ± 26.1	110.4 ± 32.6	0.05
V3	96.1 ± 25.0	107.3 ± 31.7	0.03
p	0.01	0.82	
LT3 daily dose (µg/daily)			
V0	-	-	-
V1	5.2 ± 1.4	-	-
V2	4.9 ± 1.3	-	-
V3	4.7 ± 1.3	-	-
p	<0.001	-	

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169 Footnotes: LT4: levothyroxine; LT3: liothyronine; V0: baseline visit; V1= visit at 6 weeks; V2: visit
170 at 12 weeks; V3: visit at 24 weeks. * $p<0.05$ compared to V3. Data are presented as mean ± standard
171 deviation

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174 Supplementary Table 3. Patients who reported side effects at each visit.

	LT4+LT3 group	LT4+placebo group	p
TSH<0.35 µIU/mL			
V0	11 (15.5%)	13 (18.8%)	0.38
V1	37 (56.1%)	15 (24.2%)	<0.001
V2	30 (46.2%)	15 (25.4%)	0.01
V3	21 (33.3%)	11 (19.0%)	0.06
TSH>4.94 µIU/mL			
V0	3 (4.2%)	1 (1.4%)	0.32
V1	0 (0.0%)	1 (1.6%)	0.48
V2	0 (0.0%)	2 (3.4%)	0.22
V3	1 (1,6%)	9 (15.5%)	0.05
OTHER ADVERSE EVENTS			
Insomnia			
V1	1 (1.5%)	1 (1.6%)	
V2	4 (6.2%)	3 (5.1%)	
V3	3 (4.8%)	0 (0.0%)	
Palpitations			
V1	0 (0.0%)	1 (1.6%)	
V2	3 (4.6%)	1 (1.7%)	
V3	0 (0.0%)	0 (0.0%)	
Headache			
V1	1 (1.5%)	1 (1.6%)	
V2	0 (0.0%)	1 (1.7%)	
V3	0 (0.0%)	1 (1.7%)	
Anxiety			
V1	1 (1.5%)	0 (0.0%)	
V2	3 (4.6%)	0 (0.0%)	
V3	0 (0.0%)	1 (1.7%)	
TOTAL OF OTHER ADVERSE EVENTS			
	16	10	0.77

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Footnotes: Any medical event that occurred in the subjects treated with experimental treatment (study or placebo) during the study was considered an adverse event even if it did not necessarily had a causal relationship with the treatment itself. TSH: thyroid stimulating hormone. V0: baseline visit; V1= visit at 6 weeks; V2: visit at 12 weeks; V3: visit at 24 weeks. Statistical analysis was conducted separately for adverse effects on thyroid compensation (lowering or elevation of TSH beyond reference ranges) or other events. Data are presented as the number of patients (percentages).

185 Supplementary Table 4. Distribution of *DIO2* and *MCT10* SNPs.

	WT	**Heterozygous**	**Homozygous**
***DIO2* rs225014**	AA 65 (46.4%)	GT 59 (42.1%)	GG 16 (11.4%)
***MCT10* rs17606253**	TT 108 (77.1%)	CT 28 (20.0%)	CC 4 (2.8%)

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187 Footnotes: WT: Wild Type. Data are presented as the number of patients and percentages.

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Supplementary Table 5. Distribution of *DIO2* and *MCT10* SNPs according to a recessive genetic model, in the study and the LT4+placebo groups.

	LT4+LT3 group (n=71)			**LT4+placebo group** (n=69)		
	WT	**Heterozygous**	**Homozygous**	**WT**	**Heterozygous**	**Homozygous**
***DIO2*-rs225014**	35 (49%)	24 (34%)	12 (17%)	30 (43%)	35 (51%)	4 (6%)
***MCT10*-rs17606253**	56 (79%)	14 (20%)	1 (1%)	52 (75%)	14 (20%)	3 (5%)

Footnotes: WT: Wild Type. Data are presented as the number of patients and percentages.

195 Supplementary Table 6. Distribution of *DIO2*, *MCT10,* and combined *DIO2+MCT10* SNPs

196 according to a dominant genetic model, in the study and the LT4+placebo groups.

	LT4+LT3 group (n=71)		**LT4+placebo group** (n=69)	
	WT	**SNP carriers**	**WT**	**SNP carriers**
***DIO2*-rs225014**	35 (49.3%)	36 (50.7%)	30 (43.5%)	39 (56.5%)
***MCT10*-rs17606253**	56 (78.9%)	15 (21.1%)	52 (75.4%)	17 (24.6%)
***DIO2*-rs225014 + *MCT10*-rs17606253**	61 (85.9%)	10 (14.1%)	58 (84.1%)	11 (15.9%)

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198 Footnotes: WT: Wild Type. Data are presented as the number of patients and percentages.

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Supplementary table 7. Subjects' characteristics at baseline according to the genotype of *DIO2*, *MCT10*, *DIO2+MCT10* (dominant model).

	DIO2 **WT** (n=65)	***DIO2*** **Variant** (n=75)	**p**	***MCT10*** **WT** (n=108)	***MCT10*** **Variant** (n=32)	**p**	***DIO2+MCT10*** **WT** (n=119)	***DIO2+MCT10*** **Variant** (n=21)	**p**
TSH, microUI/mL	1.9 (0.0-3.0)	1.4 (1.0-2.0)	0.30	0.9 (0.0-9.3)	1.2 (0.2-8.4)	0.55	0.9 (0.0-9.3)	1.2 (0.2-4.0)	0.57
fT4, pg/mL	10.8 (8.9-14.6)	10.2 (8.6-11.9)	0.85	11.3 (7.6-16.4)	11.9 (8.5-25.2)	0.24	11.4 (7.6-25.2)	12.0 (8.5-16.2)	0.52
fT3, pg/mL	2.8 (2.5-3.3)	3.0 (2.4-3.9)	0.99	3.0 (2.2-3.9)	3.0 (2.4-3.9)	0.76	3.0 (2.2-3.9)	3.0 (2.4-3.9)	0.41
fT3/fT4*	0.2 (0.2-0.3)	0.3 (0.3-0.4)	0.99	0.3 (0.2-0.4)	0.3 (0.1-0.3)	0.26	0.3 (0.1-0.4)	0.2 (0.2-0.3)	0.50
HYPOTHYROIDISM-RELATED SYMPTOMS REPORTED IN ANAMNESIS									
Asthenia n (%)	29 (38.7)	36 (48)	0.15	55 (50.9)	16 (50)	0.90	61 (51.3)	10 (47.6)	0.18
Weight gain n (%)	31 (41.3)	32 (42.7)	0.60	48 (44.4)	15 (46.9)	0.84	54 (45.4)	9 (42.9)	0.96
Impaired memory and concentration n (%)	26 (34.7)	23 (30.7)	0.27	37 (34.2)	12 (37.5)	0.76	43 (36.1)	6 (28.6)	0.78
Dry skin and hair changes n (%)	19 (25.3)	16 (21.3)	0.30	26 (24.1)	9 (28.1)	0.66	30 (25.2)	16 (76.2)	0.85
Cold intolerance n (%)	3 (4)	2 (2.7)	0.56	4 (3.7)	1 (3.1)	0.86	5 (4.1)	0 (0.0)	0.60

ThyPRO QUESTIONNAIRE SCORES									
Goitre symptoms	17.0 (2.3 – 25.0)	15.9 (9.1 – 22.7)	0.47	6.8 (0.0-52.3)	6.8 (0.0-40.9)	0.71	6.8 (0.0-52.3)	4.5 (0.0-40.9)	0.51
Hyperthyroidism symptoms	12.5 (3.1 – 62.5)	25.0 (21.9 – 28.1)	0.80	15.6 (0.0-78.1)	18.8 (3.1-75.0)	0.30	15.6 (0.0-78-1)	18.8 (3.1-75.0)	0.21
Hypothyroidism symptoms	12.5 (6.2 -37.5)	15.6 (6.2 – 25.0)	0.95	18.8 (0.0-62.5)	25.0 (0.0-81.3)	0.70	18.8 (0.0-68.8)	25.0 (0.0-81.3)	0.66
Tiredness symptoms	7.1 (3.6 – 71.4)	21.4 (10.7 – 32.1)	0.67	10.7 (0.0-71.4)	10.7 (0.0-75.0)	0.53	10.7 (0.0-71.4)	14.3 (0.0-75.0)	0.44
Cognitive symptoms	18.7 (8.3 – 91.7)	25.0 (16.7 – 33.3)	0.13	20.8 (0.0-91.7)	16.7 (0.0-100.0)	1.00	20.8 (0.0-91.7)	16.7 (0.0 – 100.0)	0.88
Anxiety symptoms	35.4 (4.2 – 70.8)	45.8 (33.3-59.3)	0.74	25.0 (0.0-100.0)	22.9 (0.0-87.5)	0.39	25.0 (0.0-100.0)	20.8 (0.0-87.5)	0.85
Depressivity symptoms	46.4 (25.0-67.9(	50.0 (39.3-60.7)	0.42	28.6 (0.0-75.0)	28.6 (10.7-96.4)	0.98	28.6 (0.0-75.0)	21.4 (10.7-96.4)	0.87
Emotional susceptibility symptoms	34.7 (27.8-83.3)	50.0 (47.2-52.8)	0.55	30.6 (5.6-88.9)	25.0 (0.0-97.2)	0.24	30.6 (5.6-88.9)	22.2 (0.0-97.2)	0.34
Impaired social life	15.6 (0.0-56.2)	46.9 (43.7-50.0)	0.52	6.3 (0.0-62.5)	6.3 (0.0-62.5)	0.90	6.3 (0.0-62.5)	6.3 (0.0-62.5)	0.74
Impaired daily life	2.1 (0.0-41.7)	22.9 (16.7-29.2)	0.91	4.2 (0.0-66.7)	4.2 (0.0-70.8)	0.67	4.2 (0.0-66.7)	6.3 (0.0-70.8)	0.78
Impaired sex life	6.2 (0.0-62.5)	43.7 (37.5-50.0)	0.72	12.5 (0.0-100.0)	12.5 (0.0-100.0)	0.36	12.5 (0.0-100.0)	18.8 (0.0-100.0)	0.37
Cosmetic complaints	14.6 (0.0-45.8)	37.5 (33.3-41.7)	0.38	8.3 (0.0 -83.3)	8.3 (0.0-87.5)	0.70	8.3 (0.0-83.3)	12.5 (0.0-87.5)	0.28
Item 12	25.0 (0.0-100.0)	0.0 (0.0-75.0)	0.87	25.0 (0.0-100.0)	0.0 (0.0-100.0)	0.46	25.0 (0.0-100.0)	0.0 (0.0-100.0)	0.71
TISSUE MARKERS OF THYROID HORMONE ACTION									

Osteocalcin, ng/mL	17.3 (12.7-21.8)	15.2 (9.4-21.1)	0.80	16.9 (6.1-33.8)	18.4 (9.9-25.6)	0.39	17.2 (6.1-33.8)	19.1 (9.9-25.6)	0.60
Bone alkaline phosphatase, µg/L	15.2 (12.5-17.1)	8.8 (6.7-11.0)	0.93	10.6 (4.1-24.2)	12.3 (5.1-17.1)	0.26	10.9 (4.1-24.2)	12.4 (5.1-17.1)	0.49
CTX, ng/dL	9.0 (0.0-47.0)	8.0 (0.0-30.0)	0.69	8.0 (0.0-47.0)	10.0 (3.0-32.0)	0.20	9.0 (0.0-47.0)	8.0 (3.0-21.0)	0.37
SHBG, nmol/L	33.2 (22.4-77.3)	33.1 (25.0-41.3)	0.10	43.5 (10.6 – 147.4)	42.3 (17.6-206.7)	0.87	43.5 (10.6-147.4)	41.3 (17.6-206.7)	0.22
Total cholesterol, mg/dL	206.5 (191.0-268.0)	232.5 (218.0-247.0)	0.90	203.0 (93.0-309.0)	197.5 (156.0-296.0)	0.68	202.5 (93.0-309.0)	198.0 (157.0)	0.81
Triglycerides, mg/dL	70.5 (44.0-199.0)	77.5 (65.0-90.0)	0.20	87.0 (33.0-549.0)	92.0 (41.0-156.0)	0.82	86.0 (33.0-549.0)	93.5 (54.0-156.0)	0.19
HDL-CH, mg/dL	45.5 (41.0-58.0)	53.0 (45.0-61.0)	0.30	49.0 (21.0-89.0)	54.0 (31.0-70.0)	0.07	50.0 (21.0-89.0)	55.0 (31.0 – 68.0)	0.41

Footnotes: WT: Wild Type; TSH: Thyroid Stimulating Hormone; fT4: free-thyroxine; fT3: free-triiodothyronine; CTX: C-terminal telopeptide of type 1 collagen; SHBG: Sex Hormone Binding Globulin; HDL-CH: High-Density Lipoprotein cholesterol. Data are presented as median (minimum-maximum) or the number of patients (percentages). Data were analysed using the Kruskal-Wallis test and χ-square test. p was considered significant when <0.05. *: the ratio ft3/ft4 is an additional exploratory outcome, not predefined on clinicaltrials.gov.

Supplementary table 8. Characteristics of subjects in the LT4+LT3 group at V3 according to the genotype of *DIO2*, *MCT10*, *DIO2+MCT10* (dominant model).

	DIO2 **WT** (n=30)	***DIO2*** **Variant** (n=33)	**p**	***MCT10*** **WT** (n=49)	***MCT10*** **Variant** (n=14)	**p**	***DIO2+MCT10*** **WT** (n=54)	***DIO2+MCT10*** **Variant** (n=9)	**p**
TSH, micro UI/mL	0.7 (0.0-4.7)	0.5 (0.0-25.6)	0.11	0.6 (0.0-25.6)	0.7 (0.0-3.4)	0.18	0.6 (0.0-25.6)	0.5 (0.0-3.4)	0.31
fT4, pg/mL	9.7 (6.6-18.0)	10.1 (7.4-17.7)	0.50	10.4 (6.6-17.7)	9.7 (7.5-18.0)	0.68	10.6 (6.6-18.0)	9.7 (7.5-12.2)	0.22
fT3, pg/mL	3.2 (2.1-4.6)	3.2 (2.2-4.6)	0.95	3.1 (2.1-4.6)	3.4 (2.4-4.6)	0.32	3.2 (2.1-4.6)	3.2 (2.4-4.6)	0.46
fT3/fT4*	0.3 (0.2-0.6)	0.3 (0.2-0.6)	0.83	0.3 (0.2-0.6)	0.3 (0.2-0.6)	0.36	0.3 (0.2-0.6)	0.3 (0.2-0.6)	0.50
HYPOTHYROIDISM-RELATED SYMPTOMS REPORTED IN ANAMNESIS									
Asthenia, n (%)	10 (33.3)	21 (63.6)	0.02	26 (53.1)	5 (35.7)	0.25	27 (50.0)	4 (44.4)	0.15
Weight gain, n (%)	14 (46.7)	16 (48.5)	0.88	22 (44.9)	8 (57.1)	0.42	25 (46.3)	5 (55.5)	0.83
Impaired memory and concentration, n (%)	13 (43.3)	10 (30.3)	0.28	17 (34.7)	6 (42.9)	0.58	20 (37.0)	3 (33.3)	0.89
Dry skin and hair changes, n (%)	9 (30)	7 (21.2)	0.42	11 (22.4)	5 (35.7)	0.31	13 (24.1)	3 (33.3)	0.69

Cold intolerance, n (%)	1 (3.3)	1 (3.0)	0.94	2 (4.1)	0 (0.0)	0.44	2 (3.7)	0 (0.0)	0.84
ThyPRO QUESTIONNAIRE SCORES									
Goitre symptoms	5.7 (0.0 – 36.4)	4.5 (0.0-50.0)	0.76	4.5 (0.0-50.0)	6.8 (0.0-20.5)	0.57	4.5 (0.0-59.4)	5.7 (0.0-20.5)	0.74
Hyperthyroidism symptoms	9.4 (0.0 – 59.4)	21.9 (0.0-43.8)	0.10	15.6 (0.0-59.4)	21.9 (0.0-37.5)	0.32	14.1 (0.0-59.4)	25.0 (0.0-37.5)	0.11
Hypothyroidism symptoms	12.5 (0.0-50.0)	12.5 (0.0-93.8)	0.75	12.5 (0.0-56.3)	18.8 (0.0-43.8)	0.79	12.5 (0.0-93.8)	18.8 (0.0-37.5)	0.84
Tiredness symptoms	10.7 (0.0-64.3)	7.1 (0.0-60.7)	0.63	10.7 (0.0-64.3)	7.1 (0.0-35.7)	0.20	10.7 (0.0-64.3)	10.7 (0.0-35.7)	0.93
Cognitive symptoms	16.7 (0.0-83.3)	16.7 (0.0-50.0)	0.98	16.7 (0.0-83.3)	16.7 (0.0-37.5)	0.64	16.7 (0.0-83.3)	18.8 (0.0-50.0)	0.96
Anxiety symptoms	12.5 (0.0-50.0)	14.6 (0.0-62.5)	0.89	12.5 (0.0-62.5)	12.5 (0.0-50.0)	0.86	12.5 (0.0-62.5)	18.8 (0.0-50.0)	0.55
Depressivity symptoms	21.4 (7.1-64.3)	21.4 (7.1-60.7)	0.79	21.4 (7.1-64.3)	21.4 (7.1-46.4)	0.83	21.4 (7.1-64.3)	16.1 (7.1-46.4)	0.96
Emotional susceptibility symptoms	20.8 (5.6-55-6)	23.6 (2.8-69.4)	0.62	22.2 (2.8-69.4)	22.2 (8.3-58.3)	0.56	22.2 (2.8-69.4)	23.6 (8.3-58.3)	0.90
Impaired social life	0.0 (0.0-43.8)	6.3 (0.0-37.5)	0.20	6.3 (0.0-43.8)	0.0 (0.0-37.5)	0.60	6.3 (0.0-43.8)	3.1 (0.0-37.5)	0.93
Impaired daily life	4.2 (0.0-41.7)	8.3 (0.0-45.8)	0.18	4.2 (0.0-45.8)	4.2 (0.0-29.2)	0.97	4.2 (0.0-45.8)	6.3 (0.0-29.2)	0.81
Impaired sex life	12.5 (0.0-87.5)	12.5 (0.0-100.0)	0.70	12.5 (0.0-100.0)	18.8 (0.0-87.5)	0.274	12.5 (0.0-100.0)	25.0 (12.5-87.5)	0.10

Cosmetic complaints	4.2 (0.0-54.2)	4.2 (0.0-75.0)	0.27	4.2 (0.0-75.0)	12.5 (0.0-37.5)	0.127	4.2 (0.0-75.0)	25.0 (0.0-37.5)	0.12
Item 12	0.0 (0.0-75.0)	0.0 (0.0-75.0)	0.45	0.0 (0.0-75.0)	12.5 (0.0-50.0)	0.536	0.0 (0.0-75.0)	12.5 (0.0-50.0)	0.81
TISSUE MARKERS OF THYROID HORMONE ACTION									
Osteocalcin, ng/mL	19.0 (12.1-26.6)	17.8 (7.9-30.6)	0.42	18.1 (8.6-30.6)	20.0 (7.9-26.4)	0.33	18.7 (8.6-30.6)	20.1 (7.9-26.4)	0.54
Bone alkaline phosphatase, mcg/L	11.1 (6.3-21.8)	12.5 (4.7-20.2)	0.78	10.8 (4.7-21.8)	14.5 (6.7-19.1)	0.04	11.1 (4.7-21.8)	14.7 (6.7-19.1)	0.09
CTX, ng/dL	85.0 (0.0-44.0)	10.5 (3.0-60.0)	0.68	30.0 (0.0-44.0)	12.0 (0.0-60.0)	0.28	9.5 (0.0-44.0)	10.5 (3.0-60.0)	0.67
SHBG, nmol/L	51.8 (18.8-100.0)	43.1 (13.4-109.7)	0.90	49.4 (13.4-109.7)	40.9 (24.2-94.9)	0.97	51.5 (13.4-109.7)	37.8 (24.2-94.9)	0.24
Total cholesterol, mg/dL	222.0 (141.0-296.0)	205.0 (129.0-269.0)	0.26	214.0 (129.0-296.0)	200.5 (169.0-255.0)	0.43	213.0 (129.0-296.0)	200.0 (180.0-255.0)	0.76
Triglycerides, mg/dL	74.0 (39.0-477.0)	75.0 (7.9-189.0)	0.85	76.0 (7.9-477.0)	74.0 (42.0-131.0)	0.62	74.0 (7.9-477.0)	77.0 (60.0-131.0)	0.44
HDL-CH, mg/dL	57.0 (32.0-90.0)	51.0 (34.0-90.0)	0.16	52.0 (32.0-90.0)	56.5 (41.0-64.0)	0.67	55.0 (32.0-90.0)	55.0 (41.0-64.0)	0.74

Footnotes: WT: Wild Type; TSH: Thyroid Stimulating Hormone; fT4: free-thyroxine; fT3: free-triiodothyronine; CTX: C-terminal telopeptide of type 1 collagen; SHBG: Sex Hormone Binding Globulin; HDL-CH: High-Density Lipoprotein cholesterol. Data are presented as median

(minimum-maximum) or the number of patients (percentages). Data were analysed using the Kruskal-Wallis test and χ-square test. p was considered significant when <0.05. *: the ratio ft3/ft4 is an additional exploratory outcome, not predefined on clinicaltrials.gov.