Long-term treatment of Cushing's disease with pasireotide: 5-year results from an open-label extension study of a Phase III trial

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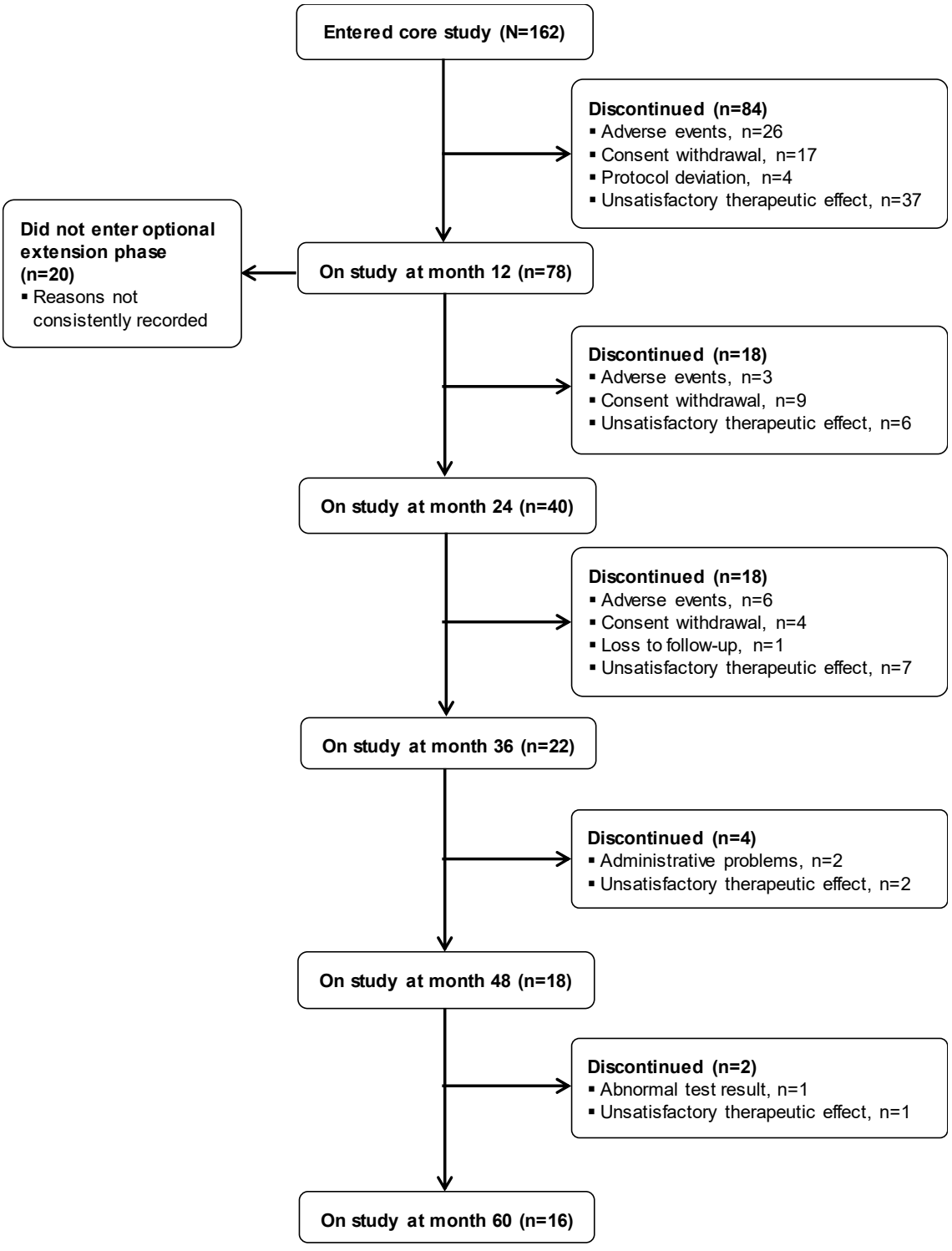
Supplementary appendix

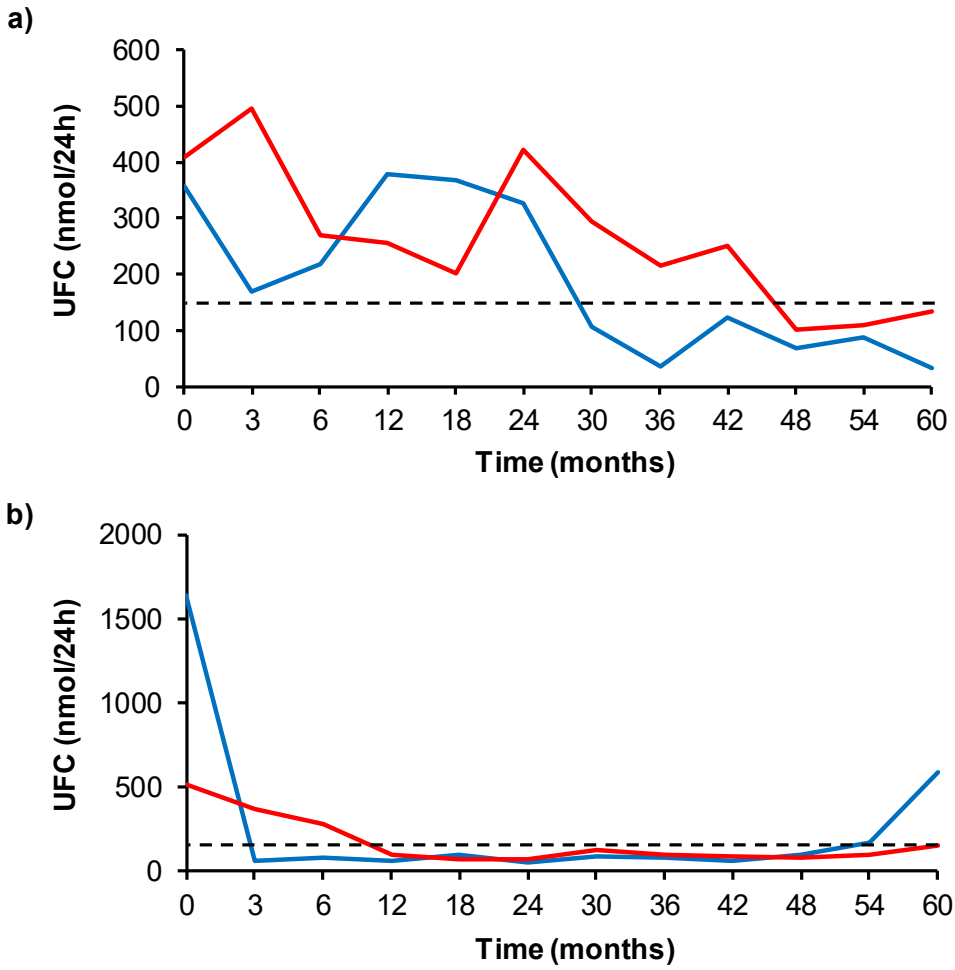
Assay details

UFC values were determined by high-performance liquid chromatography (Alliance® 2795 High Throughput System, Waters Corp, Milford, MA, USA; normal UFC range: 30–145 nmol/24h [10.8–52.5 µg/24h]). All samples were analysed by central laboratories (Eurofins Medinet BV, Breda, The Netherlands; CRL Medinet Inc, Lenexa, KS, USA; and Eurofins Technology Services [Suzhou] Co Ltd, Suzhou, China). Blood samples were tested for serum cortisol (assay: ADVIA Centaur® CP Immunoassay System, Siemens Healthcare Diagnostics Inc, Tarrytown, NY, USA) and plasma ACTH (assay: Immulite® 2000 ACTH kit, DPC, Los Angeles, CA, USA). Saliva samples were tested for salivary cortisol (assay: cortisol ELISA RE52611, IBL-Hamburg GmbH, Germany).

Supplementary Fig. 1 Reasons for patient discontinuation by treatment year

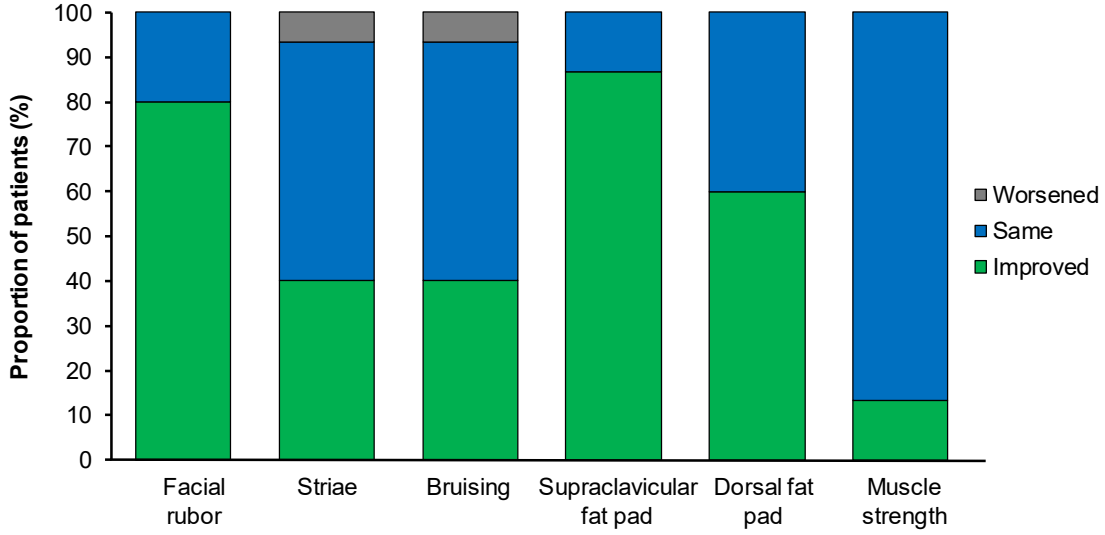


Supplementary Fig. 2 UFC levels from baseline up to month 60 in patients who were (a) uncontrolled at month 12 but controlled at month 60 (n=2) and (b) controlled at month 12 but partially controlled at month 60 (n=2)



Dashed line represents ULN for UFC (145 nmol/24h). Data represent actual UFC values from baseline to month 60 for individual patients

Supplementary Fig. 3 Proportion of patients with a shift in signs of Cushing's disease at month 60 from baseline



Facial rubor, striae, bruising and fat pads were assessed by a blinded reviewer using photographs (0=no signs, 1=mild, 2=moderate, 3=severe). Muscle strength was assessed according to the patient's ability to stand from a low seated position with arms extended (0=able to stand easily with arms extended, 1=able to stand after several efforts without using arms as assistance, 2=able to stand by using arms as assistance, 3=completely unable to stand). Fifteen patients had evaluable measurements at both month 60 and baseline

Supplementary Table 1 Changes in pituitary tumour volume in patients with evaluable measurements at baseline

Patient	Baseline, cm^3	Last available assessment, cm^3	Change to last post-baseline assessment, cm^3
1	0.20	0.03	−0.16
2	0.17	0.03	−0.14
3	0.10	0.36	+0.26
4	0.06	0.10	+0.04
5	0.04	0.09	+0.05
6	0.02	0.00	−0.02

Supplementary Table 2 CTCAE grade of AEs related to hyperglycaemia, the gallbladder/biliary tract, the liver, or bradycardia at first occurrence and worst value at any time after first occurrence (overall population)

		AE reported	Worst reported AE grade after first occurrence			
First reported		**once**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
AE grade	**n**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Bradycardia related						
Grade 1	19	14 (73.7)	4 (21.1)	0	1 (5.3)	0
Grade 2	5	2 (40.0)	2 (40.0)	0	1 (20.0)	0
Grade 3	1	1 (100.0)	0	0	0	0
Grade 4	0	0	0	0	0	0
Total	*25*	*17*	*6*	*0*	*2*	*0*
Gallbladder and biliary tract related						
Grade 1	48	31 (64.6)	10 (20.8)	2 (4.2)	3 (6.3)	2 (4.2)
Grade 2	12	5 (41.7)	3 (25.0)	3 (25.0)	1 (8.3)	0
Grade 3	1	1 (100.0)	0	0	0	0
Grade 4	0	0	0	0	0	0
Total	*61*	*37*	*13*	*5*	*4*	*2*
Hyperglycaemia related						
Grade 1	56	20 (35.7)	12 (21.4)	15 (26.8)	9 (16.1)	0
Grade 2	44	20 (45.5)	5 (11.4)	8 (18.2)	11 (25.0)	0
Grade 3	20	8 (40.0)	1 (5.0)	7 (35.0)	4 (20.0)	0
Grade 4	2	0	0	1 (50.0)	1 (50.0)	0
Total	*122*	*48*	*18*	*31*	*25*	*0*
Liver safety related						
Grade 1	15	7 (46.7)	7 (46.7)	1 (6.7)	0	0
Grade 2	9	2 (22.2)	1 (11.1)	3 (33.3)	3 (33.3)	0
Grade 3	4	1 (25.0)	1 (25.0)	0	2 (50.0)	0
Grade 4	0	0	0	0	0	0

Total	*28*	*10*	*9*	*4*	*5*	*0*

Two bradycardia-, four gallbladder/biliary-, 20 hyperglycaemia-, and three liver-related AEs worsened to CTCAE grade 3 after the first event; two gallbladder/biliary-related AEs worsened to CTCAE grade 4 (Table 3). Worst reported CTCAE grades after first occurrence were lower than at the first reported event in a number of patients (bradycardia, n=2; gallbladder/biliary tract, n=3; hyperglycaemia, n=15; liver safety, n=2)