

# Adherence and Long-term Outcomes of Therapy in Pediatric Subjects in Greece using easypod™ Electromechanical Device for Growth Hormone Treatment: The Phase IV Multicentre easypod™ Connect Observational Study (ECOS)

E. Charmandari<sup>1</sup>, S. Michalakos<sup>2</sup>, D. Sakellariou<sup>3</sup>, E. Koledova<sup>4</sup>, G. Chrousos<sup>1</sup><sup>1</sup>Division of Endocrinology, Metabolism and Diabetes, 1st Dept. Pediatrics, National and Kapodistrian University of Athens, Aghia Sophia Children's Hospital, Athens, Greece;<sup>2</sup>Department of Endocrinology - Growth and Development, P. & A. Kyriakou Children's Hospital, Athens, Greece; <sup>3</sup>Merck S.A., Marousi, Athens, Greece; <sup>4</sup>Merck KGaA, Darmstadt, Germany

\*An affiliate of Merck KGaA, Darmstadt Germany

## INTRODUCTION

- The easypod™ auto-injector device is designed to make daily administration of recombinant human growth hormone (r-hGH) comfortable and easier to patients by delivering pre-set doses of r-hGH (Saizen®, Merck KGaA, Darmstadt, Germany).
  - Furthermore, easypod™ is integrated into an eHealth ecosystem where adherence data are available to healthcare professionals in a convenient way through a secure web solution.
- Previous studies have indicated that adherence to growth hormone treatment is associated with improved growth outcomes<sup>1-3</sup>; however, adherence is often difficult to detect.<sup>4</sup>
- The easypod™ Connect Observational Study (ECOS) was the first global study of easypod™ and reported accurate and robust real-time adherence data in a large cohort of patients.<sup>5</sup>
  - High levels of adherence were generally maintained over time and were associated with a positive growth outcome.<sup>5</sup>
- In this analysis, we assess the adherence of Saizen® administered via easypod™ in a cohort of Greek patients from ECOS (EMR200104-520, NCT01363674).

## METHODS

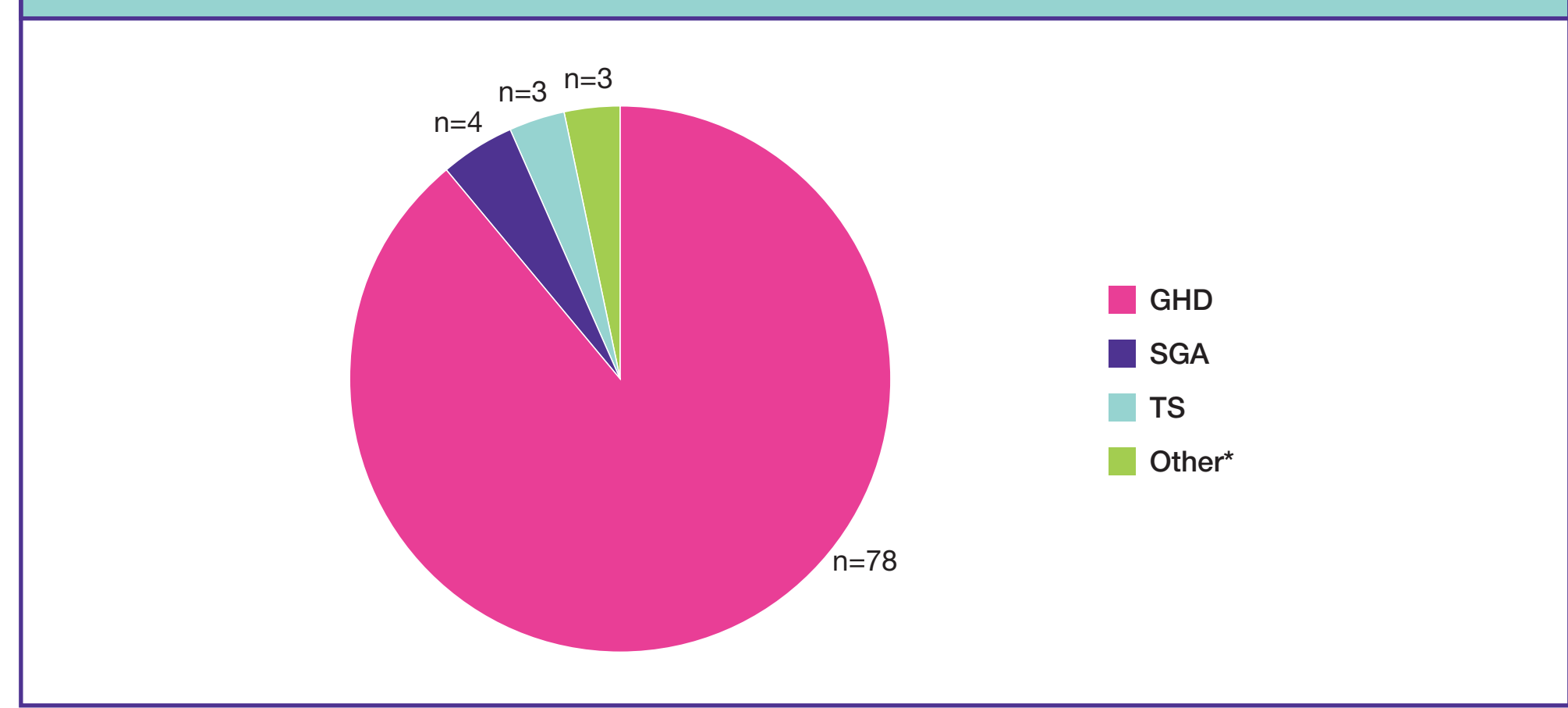
- This was an open-label, observational, longitudinal study conducted in Greece.
- Included in the study were patients aged 2–18 years, treated with Saizen® administered via easypod™ for ≥6 months and ≤3 years, with a documented start date, and no gaps in the injection data for >1 week.
- The primary endpoint was to assess mean percentage of adherence to treatment at different follow-up timepoints: 3, 6, 9, 12, 18, 24, 36 and 48 months.
  - proportion of days with injection received/days with injections planned; adherence was defined as ≥85%.
- The secondary endpoints were associated with growth outcomes including:
  - change in height and change in height standard deviation score [SDS].
  - height velocity and height velocity SDS.
  - correlation between adherence and growth outcomes (Spearman's product moment;  $r_s$ ).
  - the impact of adherence on IGF-I concentrations.
- Adherence data were primarily collected from injections recorded using easypod™ combined with physiological outcomes submitted by physicians.
- The easypod™ adherence complete analysis set (CAS) included patients with a documented start date of easypod™ usage, no gap in injection data of >1 week and height measurements were documented both at baseline and at 1 year of treatment.
  - The easypod™ adherence data analysis set (DAS) included patients from the easypod™ adherence CAS who reported adherence data for a period of ≥3 months after commencement of easypod™ use.
- The easypod™ adherence DAS was used for the main analysis, to avoid confounding the results with patients who were experimenting with easypod™ or using it for a period of <3 months.
  - All analyses were descriptive.

## RESULTS

### Patient Disposition

- Among the 180 patients enrolled, 88 were included in the CAS.
  - Among them, 78 patients had growth hormone deficiency (GHD), four were small for gestational age (SGA), three had Turner syndrome (TS) and three were either missing or had another diagnosis (Figure 1).
  - 82 patients from the CAS were GH-naïve (not previously exposed to GH treatment prior to initiating treatment with easypod™).
- From the 88 patients included in the CAS, 86 patients comprised the DAS.
  - Among them, 76 patients had GHD, four were SGA, three had TS and three were either missing or had another diagnosis.
  - 81 patients from the DAS were GH-naïve.

Figure 1. Patient Diagnoses: CAS



\*One patient had chronic renal failure/chronic kidney disease, one had short stature/slow growth and information for one was missing; CAS, complete analysis set; GHD, growth hormone deficiency; SD, standard deviation; SGA, small for gestational age; TS, Turner Syndrome

### Baseline Characteristics

- In the CAS, the median age was 11 years; patients diagnosed with SGA or TS were slightly younger than those with GHD (Table 1).

Table 1. Baseline Characteristics: CAS

Characteristic	GHD (n=78)	SGA (n=4)	TS (n=3)	Other* (n=3)	Overall (n=88)
Age, years					
Mean (SD)	10.32 (2.80)	9.00 (3.16)	8.67 (3.21)	11.00 (1.73)	10.23 (2.79)
Median	11.0	9.5	10.0	12.0	11.0
Q1; Q3	8.0; 12.0	6.5; 11.5	5.0; 11.0	9.0; 12.0	8; 12
Min; Max	4.0; 16.0	5.0; 12.0	5.0; 11.0	9.0; 12.0	4; 16
Gender, n (%)					
Male	53 (67.9)	1 (25.0)	0 (0.0)	1 (33.3)	55 (62.5)
Female	25 (32.1)	3 (75.0)	3 (100.0)	2 (66.7)	33 (37.5)
Tanner stage					
male, n (missing)	31 (22)	1 (0)	0 (0)	1 (0)	33 (22)
Tanner 1, n (%)	20 (64.5)	1 (100.0)	0 (0.0)	0 (0.0)	21 (63.6)
Tanner >1, n (%)	11 (35.5)	0 (0.0)	0 (0.0)	1 (100.0)	12 (36.4)
female, n (missing)	18 (7)	3 (0)	2 (1)	2 (0)	25 (8)
Tanner 1, n (%)	10 (55.6)	3 (100.0)	2 (100.0)	1 (50.0)	16 (64.0)
Tanner >1, n (%)	8 (44.4)	0 (0.0)	0 (0.0)	1 (50.0)	9 (36.0)
Bone age <sup>†</sup> , n (missing)	35 (0)	2 (0)	3 (0)	2 (0)	42 (0)
Mean (SD)	9.80 (2.94)	8.04 (5.60)	8.33 (3.25)	9.25 (2.47)	9.59 (2.98)
Median	11.00	8.04	8.50	9.25	10.75
Q1; Q3	8.0; 11.5	4.1; 12.0	5.0; 11.5	7.5; 11.0	7.5; 11.5
Min; Max	3.0; 14.5	4.1; 12.0	5.0; 11.5	7.5; 11.0	3.0; 14.5

\*One patient had chronic renal failure/chronic kidney disease, one had short stature/slow growth and information for one was missing; <sup>†</sup>Based on a Greulich and Pyle assessment; CAS, complete analysis set; GHD, growth hormone deficiency; SD, standard deviation; SGA, small for gestational age; TS, Turner Syndrome

- The majority of patients were in Tanner stage 1 (63.6% of male and 64.0% of female patients).
- Patients with SGA or TS generally had a lower mean bone age, according to the Greulich and Pyle assessment.

### Auxological Information

- The median height among the overall CAS population was 129.9 cm and the median height velocity was 4 cm per year (Table 2).
- The median height and height velocity were similar across the different diagnoses.

Table 2. Auxological Information: CAS

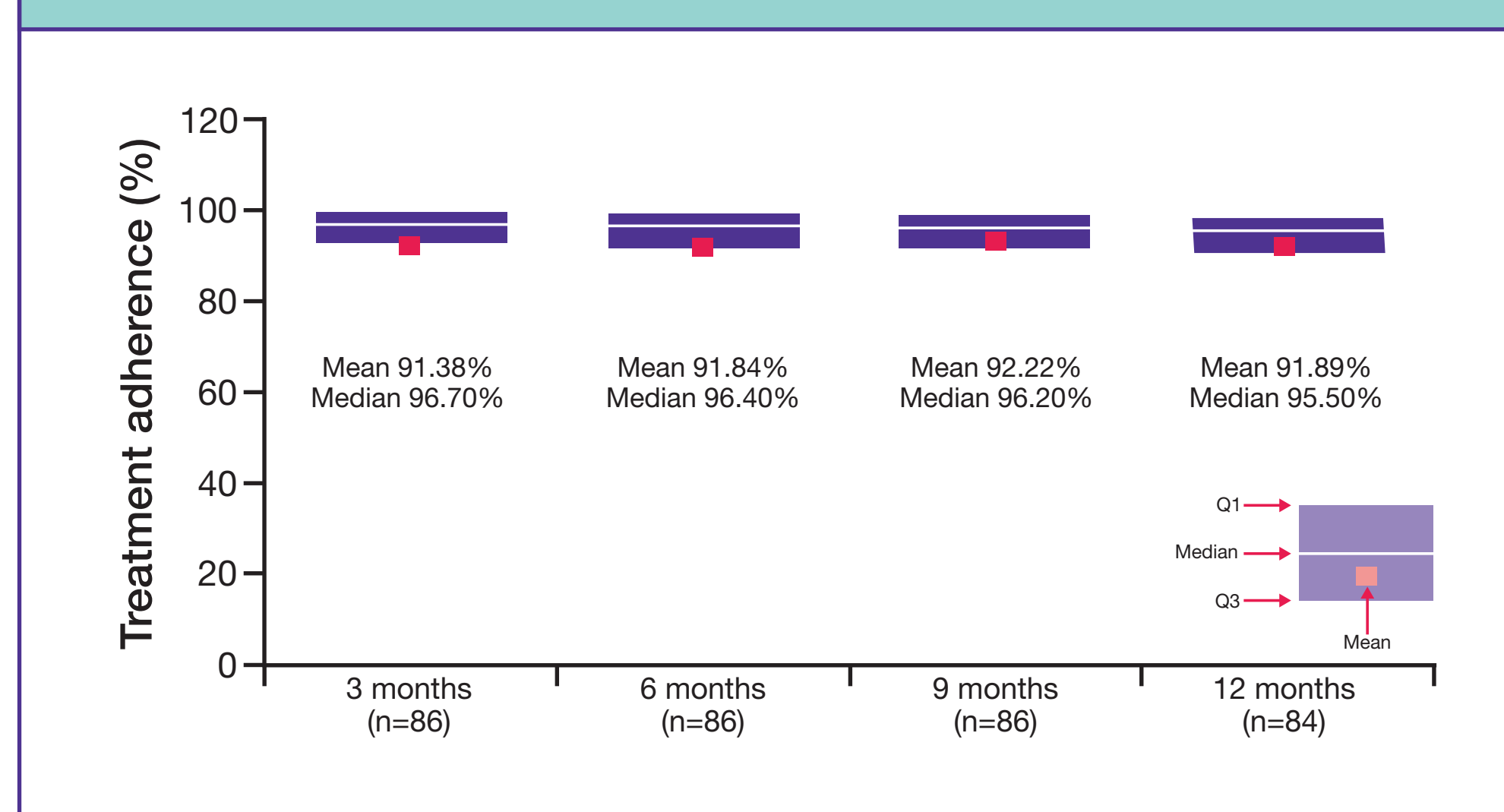
Characteristic	GHD (n=78)	SGA (n=4)	TS (n=3)	Other* (n=3)	Overall (n=88)
Gestational age (weeks), n (missing)	78 (0)	4 (0)	3 (0)	3 (0)	88 (0)
Mean (SD)	37.8 (2.3)	34.8 (3.3)	39.3 (0.6)	39.3 (1.2)	37.8 (2.4)
Median	38	36	39	40	38
Q1; Q3	37; 39	32.5; 37	39; 40	38; 40	37; 39
Min; Max	26; 40	30; 37	39; 40	38; 40	26; 40
Birth length (cm), n (missing)	73 (5)	4 (0)	3 (0)	3 (0)	83 (5)
Mean (SD)	49.2 (3.0)	45.4 (2.6)	49.3 (1.2)	51.0 (1.0)	49.1 (3.0)
Median	50	45	50	51	50
Q1; Q3	48; 51	44; 47	48; 50	50; 52	48; 51
Min; Max	33; 54	43; 49	48; 50	50; 52	33; 54
Birth weight (g), n (missing)	78 (0)	4 (0)	3 (0)	3 (0)	88 (0)
Mean (SD)	2909.8 (551.9)	1930.0 (591.8)	2783.0 (625.2)	3226.7 (517.3)	2871.8 (586.0)
Median	2995	2060	2500	3500	2935
Q1; Q3	2650; 3200	1560; 2300	2350; 3500	2630; 3550	2550; 3200
Min; Max	830; 3950	1100; 2500	2350; 3500	2630; 3550	830; 3950
Growth velocity (cm/year), n (missing)	78 (0)	4 (0)	3 (0)	3 (0)	88 (0)
Mean (SD)	3.9 (0.9)	4.5 (1.7)	4.0 (1.0)	3.8 (0.3)	3.9 (0.9)
Median	4	4	4	4	4
Q1; Q3	3.3; 4.0	3.5; 5.5	3.0; 5.0	3.5; 4.0	3.4; 4.1
Min; Max	1.6; 7.3	3.0; 7.0	3.0; 5.0	3.5; 4.0	1.6; 7.3
Height (cm), n (missing)	78 (0)	4 (0)	3 (0)	3 (0)	88 (0)
Mean (SD)	127.7 (15.6)	122.8 (20.4)	120.1 (16.8)	133.1 (10.6)	127.4 (15.6)
Median	130	127	123	137	130
Q1; Q3	115.5; 139.5	106.1; 139.50	102.1; 135.2	121.1; 141.2	115.25; 139.45
Min; Max	88.5; 158.0	97.8; 140.0	102.1; 135.2	121.1; 141.2	88.5; 158.0

\*One patient had chronic renal failure/chronic kidney disease, one had short stature/slow growth and information for one was missing; CAS, complete analysis set; GHD, growth hormone deficiency; SD, standard deviation; SGA, small for gestational age; TS, Turner Syndrome

### Treatment Adherence

- In the DAS, median adherence was 96.7% (n=86) at 3 months and remained high, at 95.5% (n=84) by 12 months (Figure 2).

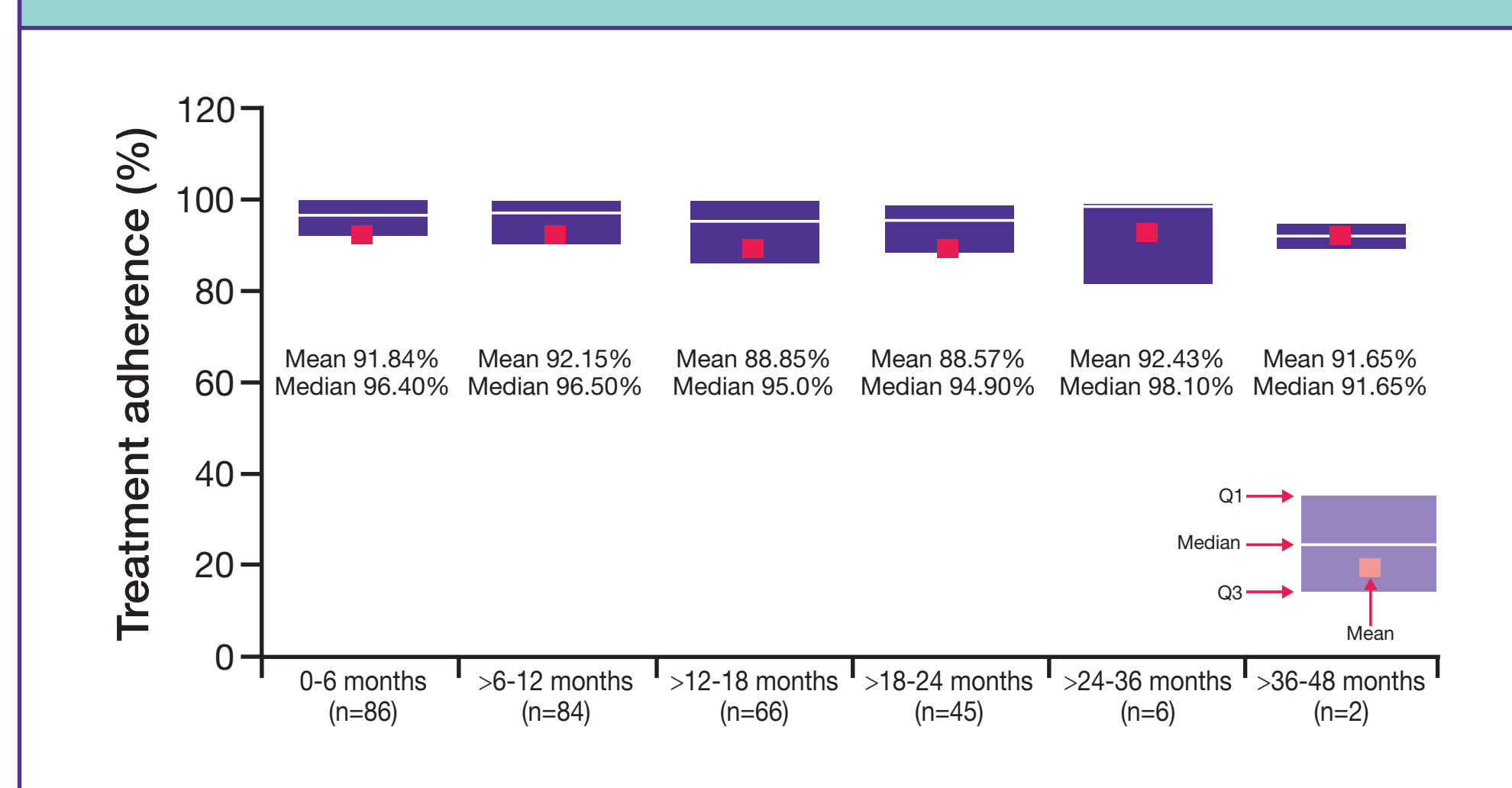
Figure 2. Treatment Adherence: DAS



DAS, data analysis set

- When analyzed in discrete interval periods, median adherence remained at >90% for up to 48 months (Figure 3).
- Treatment adherence in the GH-naïve patient subgroup and per indication were comparable with results observed in the overall DAS (data not shown).

Figure 3. Treatment Adherence by Discrete Interval Periods: DAS



DAS, data analysis set

### Growth Outcomes

- In the DAS, after 1 year of treatment, median increases in height (7.25 cm) and height SDS (0.32) were reported (Table 3).
- In terms of height velocity, a median of 7.62 cm/year was reported with a median height velocity SDS of 1.65.
- In the GH-naïve patient subpopulation, growth outcomes were similar to those in the DAS.

### IGF-I Concentrations

- The majority of patients with IGF-I data available recorded normal levels of IGF-I after 1 year of treatment (n=55 of 62; 88.7%) (Figure 4).
- 4 patients reported abnormally low and 3 patients reported abnormally high levels of IGF-I.

### Correlation of Adherence and Growth Outcomes

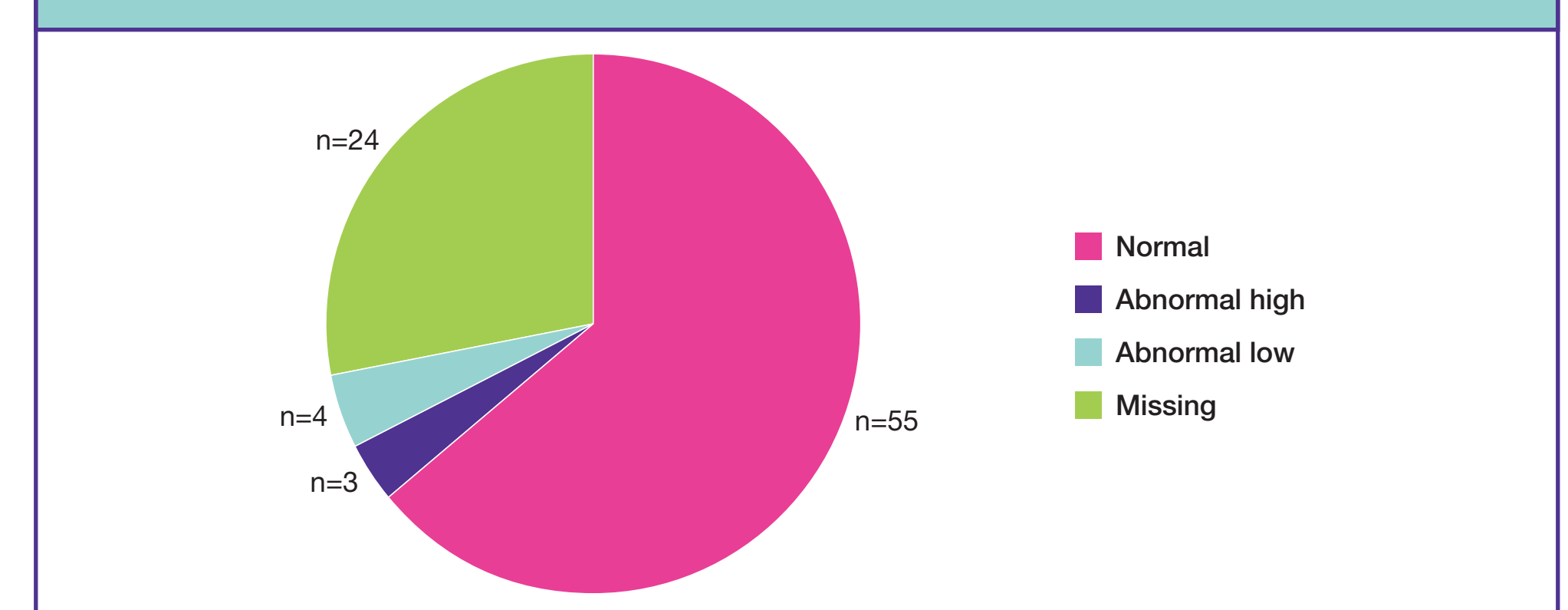
- In the overall DAS population, Spearman's product moment correlation analysis suggested a positive association between adherence and growth outcomes (change in height, change in height SDS, height velocity and height velocity SDS); however, no significant correlation was noted.
- Due to the small sample size, these results should be interpreted with caution.

Table 3. Growth Outcomes After 1 Year of Treatment

Growth Outcome	DAS (n=86)	DAS: GH-naïve (n=81)
Change in height, cm		
Mean (SD)	7.50 (2.02)	7.51 (2.03)
Median	7.25	7.30
Q1; Q3	6.00; 8.80	6.00; 8.80
Min; Max	3.3; 12.5	3.3; 12.5
Change in height SDS		
Mean (SD)	0.36 (0.27)	0.36 (0.27)
Median	0.32	0.33
Q1; Q3	0.14; 0.54	0.14; 0.54
Min; Max	-0.1; 1.1	-0.1; 1.1
Height velocity, cm/year		
Mean (SD)	7.81 (1.80)	7.83 (1.80)
Median	7.62	7.64
Q1; Q3	6.39; 9.13	6.42; 9.13
Min; Max	4.3; 13.5	4.3; 13.5
Height velocity SDS		
Mean (SD)	1.62 (2.12)	1.64 (2.12)
Median	1.65	1.72
Q1; Q3	0.17; 2.91	0.17; 2.91
Min; Max	-3.1; 6.9	-3.1; 6.9

DAS, data analysis set; GH, growth hormone; SDS, standard deviation score

Figure 4. IGF-I Status After 1 Year of Treatment: DAS



DAS, data analysis set; IGF-I, insulin-like growth factor-1

Table 4. Correlation of Adherence and Growth Outcomes After 1 Year of Treatment: DAS

Growth Outcome	GHD (n=76)	SGA (n=4)	TS (n=3)	Other* (n=3)	Overall (n=86)
Change in height, cm	74 (2)	4 (0)	3 (0)	3 (0)	84 (2)
Spearman's product moment correlation	0.186	0.600	1.000	1.000	0.207
P value	0.1125	0.4000	<0.0001	<0.0001	0.0593
Change in height SDS	74 (2)	4 (0)	3 (0)	3 (0)	84 (2)
Spearman's product moment correlation	0.217	0.000	0.500	1.000	0.233
P value	0.0635	1.0000	0.6667	<0.0001	0.0329
Height velocity, cm/year	74 (2)	4 (0)	3 (0)	3 (0)	84 (2)
Spearman's product moment correlation	0.094	0.800	1.000	1.000	0.127
P value	0.4263	0.2000	<0.0001	<0.0001	0.2514
Height velocity SDS	74 (2)	4 (0)	3 (0)	3 (0)	84 (2)
Spearman's product moment correlation	0.130	-0.400	0.500	1.000	0.143
P value	0.2679	0.6000	0.6667	<0.0001	0.1931

\*One patient had chronic renal failure/chronic kidney disease, one had short stature/slow growth and information for one was missing; CAS, complete analysis set; GHD, growth hormone deficiency; SD, standard deviation; SDS, standard deviation score; SGA, small for gestational age; TS, Turner Syndrome

## CONCLUSIONS

- This study provides the first results of a data-driven ecosystem to support adherence in patients treated with Saizen® and easypod™ Connect in Greece
- Results from this study of the Greek ECOS cohort are in agreement with the results from the global ECOS analysis
- Treatment with Saizen® administered via easypod™ led to high adherence rates with over 90% of patients adherent after 1 year
  - Similar results were observed when treatment adherence was evaluated in discrete interval periods up to 2 years
- High levels of adherence observed in this study highlight the value of easypod™ and an e-health platform for monitoring adherence in patients treated with Saizen® and supporting healthcare professionals in decision making
- Growth outcomes were improved after 1 year of treatment regardless of whether the patient was GH-naïve or not
- No significant correlation among adherence and efficacy parameters (change in height, change in height SDS, height velocity and height velocity SDS) was noted
- Normalisation of IGF-I levels was observed following 1 year of treatment

## REFERENCES

- Haverkamp et al. *Clin Ther.* 2008; **30**:307-316.
- Cutfield et al. *PLoS One.* 2011; **6**:e16223.
- Fisher and Acerini. *Horm Res Paediatr.* 2013; **79**:189-196
- Bozzola et al. *BMC Endocr Disord.* 2011; **11**:4.
- Koledova et al. *Endocr Connect.* 2018; **7**:914-923.

## ACKNOWLEDGMENTS

The authors would like to thank all the participants who contributed to this study. This study was sponsored by Merck KGaA, Darmstadt, Germany. Medical writing assistance was provided by Ricky Tsang, inScience Communications, UK, and sponsored by Merck KGaA, Darmstadt, Germany.

## DISCLOSURES

DS is an employee of Merck S.A., an affiliate of Merck KGaA, Darmstadt, Germany. EK is an employee of Merck KGaA, Darmstadt, Germany.

Copies of this poster obtained through QR (Quick Response) code are for personal use only and may not be reproduced without written permission of the authors.



GET POSTER PDF