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Adherence and long-term outcomes of therapy in pediatric subjects in Slovakia using easypod™ electromechanical device for growth hormone treatment: the Phase IV multicentre Easypod™ Connect Observational Study (ECOS)

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INTRODUCTION

- Easypod™ is the only electromechanical device for the delivery of recombinant human growth hormone (r-hGH; Saizen®) that tracks adherence.
- The easypod™ device was developed to improve patient convenience and comfort for long-term treatment with Saizen®.
- Ease and convenience of administering treatment can have a positive impact on the level of adherence, leading to more favorable growth outcomes.[1-3]
- Easypod™ prospectively records the date, dose, and time of every Saizen® adminstration to reliably monitor adherence to treatment.
- The Easypod™ Connect Observational Study (ECOS) is the first study to provide objective evidence of real-world adherence and effects on growth outcomes of the easypod™ device.
- This is the report of adherence outcomes in the cohort of ECOS patients in Slovakia.

AIMS

Primary Outcome

- To assess the level of adherence of participants receiving Saizen® via easypod™.

Secondary Outcomes

- To describe the correlation between adherence and 1-year growth outcomes (height standard deviation score (SDS) and height velocity SDS).

METHODS

Study Outline

- ECOS was an observational, open-label, Phase IV study utilizing the easypod™ device to provide objective evidence of the levels of adherence to r-hGH therapy over 5 years.
- ECOS started in November 2010 and the last participant completed in February 2016.
- In the Slovak cohort: patients were 3-19 years old, with growth hormone deficiency, born small for gestational age (SGA) and girls with Turner syndrome (TS), received Saizen® via the easypod™ electromechanical device. All patients were naïve when they started with the study.
- Patients attended one inclusion visit followed by between one and three follow-up visits per year, according to routine clinical practice.

Data Collection

- Adherence data were obtained prospectively via the easypod™ device for all subjects in the various data analysis sets (Figure 1).
- Demographic, auxological, and diagnostic data were obtained from the patients' medical notes.

Statistical Analyses

- Baseline demographics and auxological information were measured in the complete analysis set (CAS), which comprised participants from the full analysis set (FAS) who met the following conditions.
  - Easypod™ start date was available from the case report form.
  - No gap in injection data of more than one week after the start of treatment.
  - The height measurement closest to treatment start date (+/- 3 months) was available.
  - The height measurement closest to 1 year (+/- 3 months) after treatment start date was available.
- Exposure to study treatment, adherence, and the change in growth parameters were measured in the easypod™ adherence data analysis set (easypod™ adherence DAS), which consisted of all patients with adherence data available for a period of ≥3 months after enrolment in the study.
- The following indication sets were used.
  - Participants with growth hormone deficiency (GHD), those who were born SGA, those with TS, and those with other/missing indications.

RESULTS

Participants

- 2420 participants were enrolled in the ECOS study globally. **92 participants aged 3–16 years were included in the FAS in the Slovak cohort**.
  - 53 participants of the Slovak cohort were included in the CAS
  - 52 participants of the Slovak cohort were included in the easypod™ adherence DAS
- The median age in the Slovak cohort (n=92) was 9 years, which means that the majority of patients were of prepubertal age.
- 39% were female and 61% were male.
- The baseline demographics of the FAS are shown in Table 1 and baseline auxological information is shown in Table 2.
- Indications: GHD [n=36], SGA [n=48], TS [n=8]

Figure 1. Patient datasets

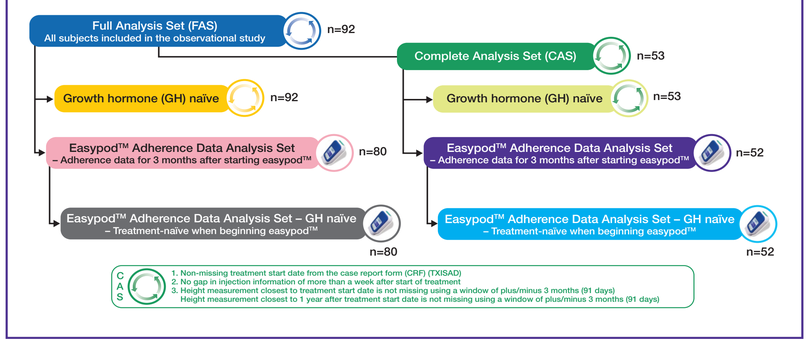


Figure 2. Indications in Slovak cohort

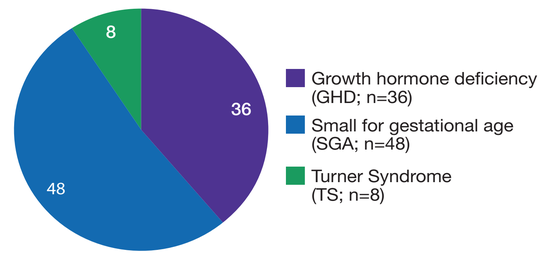


Table 1. Baseline Demographics of Full Analysis Set

	GHD (n=36)	SGA (n=48)	TS (n=8)	Overall (n=92)
Age, years				
Mean (SD)	9.72 (3.72)	8.48 (3.41)	7.25 (4.17)	8.86 (3.64)
Median	10.50	8.00	6.00	9.00
Q1; Q3	6.00; 13.00	5.00; 12.00	3.50; 11.50	5.00; 12.00
Min; Max	3.0; 16.0	4.0; 15.0	3.0; 13.0	3.0; 16.0
Sex, n (%)				
Female	7 (19.4)	21 (43.8)	8 (100)	36 (39.1)
Male	29 (80.6)	27 (56.3)	0	56 (60.9)

Table 2. Baseline Auxological Data of the Full Analysis Set

	GHD (n=36)	SGA (n=48)	TS (n=8)	Overall (n=92)
Growth velocity at GH treatment start (cm/year)				
Mean (SD)	3.24 (1.44)	3.58 (1.85)	3.88 (2.03)	3.47 (1.71)
Median	3.55	3.40	4.50	3.55
Q1; Q3	2.00; 4.00	2.40; 4.64	2.00; 5.00	2.02; 4.40
Height at GH treatment start (cm)				
Mean (SD)	125.91 (19.87)	116.66 (17.10)	111.71 (20.66)	119.85 (19.01)
Median	126.95	116.80	107.00	124.00
Q1; Q3	108.40; 144.50	101.15; 132.95	93.50; 130.00	102.00; 136.20

Adherence

- Median (Q1;Q3) treatment duration was 845 (542;1063) days and the median starting dose was 0.0318 (0.028;0.034) mg/kg.
- Overall median adherence was 92.4%.
- Overall median adherence was 95.5% to 1 year, 93% to 2 years and 83% to 3 years.
- The highest adherence rate was in the group with GHD.

Figure 3. Treatment Adherence Rates Over Time

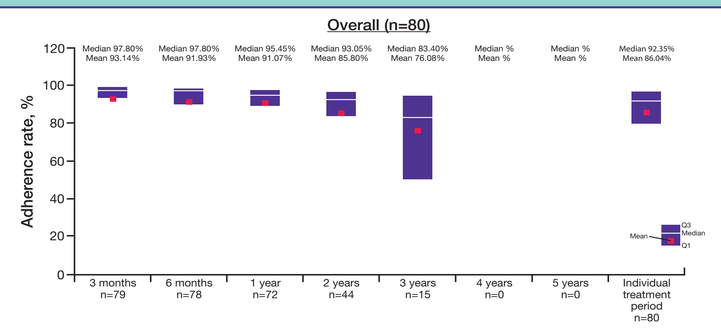
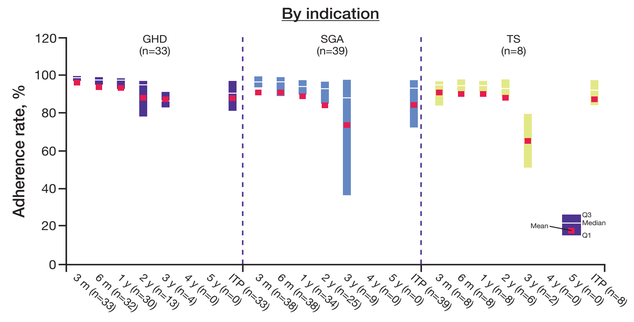


Figure 4. Treatment Adherence Rates According to the Indication



Growth Outcomes

- The 1-year median change in height SDS (Q1;Q3) was 0.49 (0.37;0.62) and the 1-year median change in height velocity SDS (Q1;Q3) was 2.53 (1.32;3.87) in FAS (n=80) (Table 3).
- Analysis at 1 year in patients who had no missing data and no gaps in treatment >1 week CAS; N=52) produced similar results:
  - Overall median adherence was 93%
  - Median change in height SDS (Q1;Q3) was 0.49 (0.37;0.62) and change in median height velocity SDS (Q1;Q3) was 2.54 (1.54;3.73)

Correlation of Growth Outcomes with Adherence at 1 Year

- Correlations were generally suggestive of a positive association, as observed for each of the indication groups, although these only reached significance for the GHD group (Table 4).
- Up to 1 year the Spearman product-moment correlation between adherence and change in height SDS was positive and significant (p=0.0143) in the subset of patients with GHD.
- These findings are based on a small sample size but are consistent with findings in global data.

Insulin–like Growth Factor 1

- Overall 1-year insulin-like growth factor 1 (IGF-1) concentrations (n=92) were within the normal range in 44 patients (88%), abnormally high in 2 (4%), and abnormally low in 4 (8%) in the FAS.

Table 3. Change in growth outcome parameters after 1 year

	GHD (n=33)	SGA (n=39)	TS (n=8)	Overall N=80
Height (cm) at Baseline				
n (missing)	25 (8)	30 (9)	5 (3)	60 (20)
Mean (SD)	129.01 (18.05)	118.83 (17.79)	118.64 (23.78)	123.06 (18.77)
Median	133.10	119.00	125.00	125.90
Q1; Q3	110.40; 144.00	100.60; 135.80	95.00; 135.00	105.95; 138.60
Change in height (cm)				
n (missing)	25 (8)	26 (13)	4 (4)	55 (25)
Mean (SD)	8.11 (1.69)	7.78 (1.68)	7.03 (1.34)	7.87 (1.66)
Median	8.00	7.70	6.55	7.70
Q1; Q3	6.90; 9.40	6.30; 8.90	6.25; 7.80	6.60; 9.20
Height SDS at Baseline				
n (missing)	25 (8)	30 (9)	5 (3)	60 (20)
Mean (SD)	-2.22 (0.74)	-2.19 (1.20)	-2.45 (1.08)	-2.23 (1.01)
Median	-1.98	-2.27	-2.17	-2.17
Q1; Q3	-2.29; -1.83	-2.70; -2.13	-3.15; -1.57	-2.71; -1.95
Change in height SDS				
n (missing)	25 (8)	26 (13)	4 (4)	055 (25)
Mean (SD)	0.54 (0.21)	0.47 (0.18)	0.42 (0.17)	0.50 (0.20)
Median	0.52	0.48	0.41	0.49
Q1; Q3	0.37; 0.75	0.37; 0.60	0.30; 0.54	0.37; 0.62
Height velocity (cm per year)				
n (missing)	25 (8)	26 (13)	4 (4)	55 (25)
Mean (SD)	9.09 (1.76)	8.56 (1.20)	7.86 (1.14)	8.75 (1.50)
Median	8.83	8.62	7.95	8.74
Q1; Q3	7.86; 9.99	7.57; 9.47	6.91; 8.81	7.58; 9.73
Height velocity SDS				
n (missing)	25 (8)	26 (13)	4 (4)	55 (25)
Mean (SD)	3.51 (3.28)	2.33 (1.58)	2.43 (1.84)	2.87 (2.54)
Median	2.59	2.39	2.49	2.53
Q1; Q3	1.73; 4.19	1.32; 2.96	0.84; 4.01	1.32; 3.87
IGF-1 standard score at Year 1, n (%)				
n (missing)	19 (14)	25 (14)	6 (2)	50 (30)
Abnormally low	2 (10.5)	2 (8.0)	0	4 (8.0)
Normal	17 (89.5)	23 (92.0)	4 (66.7)	44 (88.0)
Abnormally high	0	0	2 (33.3)	2 (4.0)

Table 4. Correlation of Adherence Rate and Growth Outcome after 1 Year

	GHD (n=33)	SGA (n=39)	TS (n=8)	Overall N=80
Change in height (cm)				
n (missing)	22 (11)	23 (16)	4 (4)	49 (31)
Spearman's product-moment correlation	0.666	0.163	0.400	0.415
P value	0.0007	0.4566	0.6000	0.0030
Change in height SDS				
n (missing)	22 (11)	23 (16)	4 (4)	49 (31)
Spearman's product-moment correlation	0.514	-0.003	0.200	0.270
P value	0.0143	0.9893	0.8000	0.0608
Height velocity (cm/year)				
n (missing)	22 (11)	23 (16)	4 (4)	49 (31)
Spearman's product-moment correlation	0.540	0.006	0.000	0.308
P value	0.0094	0.9785	1.0000	0.0313
Height velocity SDS				
n (missing)	22 (11)	23 (16)	4 (4)	49 (31)
Spearman's product-moment correlation	0.180	-0.220	0.400	0.015
P value	0.4215	0.3135	0.6000	0.9173

CONCLUSIONS

1. **Overall median adherence to treatment up to 3 years was >90%.**
2. **Growth outcomes were clinically meaningful and similar among all patients.**
3. **A positive association was seen between adherence and growth outcomes at 1 year for patients with GHD.**
4. **IGF-1 concentrations generally appeared to be maintained within normal limits.**
5. **ECOS has produced useful insights into growth response and shows that easypod™ can help physicians to identify and manage patients with inadequate adherence and poor growth response.**

USED ABBREVIATIONS

r-hGH, recombinant human growth hormone; SD, standard deviation; SDS, standard deviation score; CAS, complete analysis set; FAS, full analysis set; DAS, data analysis set; GHD, growth hormone deficiency; SGA, small for gestational age; TS, turner syndrome; IGF-1, insulin-like growth factor 1

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DISCLOSURES

LK, SB, MČ, AD, JF, SK, EM, ZP, LT and VŠ have no conflicts of interest to declare. MB is an employee of Merck s.r.o., an affiliate of Merck KGaA, Darmstadt Germany.

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GH and IGFs

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