for chronological age (CA) with mean BA/CA ratios of approximately 1 in both 33 μg/kg/day (1.01) and 67 μg/kg/day (1.09) groups.
Conclusions: Long-term GH therapy in short Japanese children born SGA results in a dose-dependent increase in IGF-I that positively correlates with changes in height SDS. No acceleration of BA was observed with either GH dose tested.

P03-35
Elucidation of mechanism underlying growth retardation caused by human growth hormone mutant E74K

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Between 5% and 30% of patients with isolated GH deficiency (IGHD) have an affected first-degree relative, which suggests a genetic etiology. The typical autosomal dominant IGHD (IGHD II) is caused by splice site mutations leading to deletion of aa 32–71. This 17.5 kDa GH is retained in endoplasmic reticulum, disrupts the transport through the Golgi apparatus and impairs both GH and other hormone trafficking. However, IGHD II patients with subtle mutations in GH1 gene, such as missense or small deletion mutations might show relatively mild growth retardation or variable clinical severity. The underlying molecular mechanism is not fully understood and may vary among the different mutations. The missense mutation E74K is one of the heterozygous mutations found in individuals with short stature selected by the modulated clinical criteria. Using the modulated criteria may improve disclosure of subtle lesions in GH1 gene of individuals with short stature. We have produced and studied E74K mutant GH in vitro. Incubation of the E74K GH in trypsin solution did not present any altered stability. Binding analysis of the E74K GH to the extracellular domain of the GH receptor showed no change of the affinity compared to wildtype GH, However, the concentration of the E74K GH in the supernatant of the transfected HEK 293 cells was dramatically reduced (48.7 %, $P < 0.05$) in comparison with wildtype GH, as determined by time resolved fluorescent sandwich immunoassays with specifically selected monoclonal antibodies and confirmed by Western blot analysis. Co-expression of wildtype and E74K GH also exhibited reduced total GH concentration. Furthermore, in proliferation assay with full length GHR expressing Baf/B03 cell line, the dose-response elicited by the E74K GH was impaired versus wildtype hGH as demonstrated by a higher EC50 and the reduced maximal effect. The intracellular production of E74K and wildtype GH as well as the secretion into cell supernatant are currently under the detailed investigation by use of the AtT-20 mouse pituitary cell line.

P03-36
Sustained effect of Insulin-Like Growth Factor-I (IGF-I)-based dosing of Growth Hormone Treatment (GHT) in children: Comparative analysis of data from a randomized trial and the ANSWER Program®

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Background: In a randomized controlled trial (RCT) in pediatric patients with short stature, IGF-I-targeted growth hormone (GH) dosing resulted in a more robust growth response than was observed with conventional weight-based dosing (Cohen et al JCEM 2007, 2010). Some of the GH-deficient (GHD) patients who participated in this RCT were subsequently followed in the American Norditropin Studies: Web-Enabled Research (ANSWER) Program®, a US-based GH registry.
Objective: To assess the sustainable effects of IGF-I-based GH dosing on change in height standard deviation score (ΔHSDS) and GH dose requirements over time in GHD patients who previously participated in the RCT, compared with GHD patients treated in the ANSWER Program®.
Methods: GHD patients (n = 28) from the 2-year RCT were subsequently enrolled in the ANSWER Program®. In the RCT, patients were randomized to an IGF-I-based GH dosing regimen titrated to an IGF-I SDS target of either 0 (RCC1, n = 14) or +2 (RCC2, n = 11). These patients were followed up in the ANSWER® registry on conventional GHT after the RCT ended. Baseline characteristics and treatment-induced changes in growth parameters from the RCT patients were compared with that of GHD patients enrolled in the ANSWER Program® (GHD-ANSWER, n = 4994).
Results: At baseline, RCT patients were younger with more severe short stature than the GHD-ANSWER patients: mean±SD age (y) was 6.5±2.4 y for RCT, and 10.9±3.5 y for GHD-ANSWER; HSDS was −2.6±0.6 for RCT, and −2.1±0.9 for GHD-ANSWER. RCT patients had significantly higher ΔHSDS than GHD-ANSWER patients at year 2 of the RCT (end of trial) and this effect was maintained through year 4 (year 2 for RCT patients in ANSWER) (Table 1). Patients randomized to RCC2 had a significantly greater ΔHSDS than those in RCC1 (Table 1) at years 2 and 3 (year 1 for RCT patients in ANSWER). The RCC2 group received a higher mean GH dose (mcg/kg/day) than RCC1 during the RCT (RCC2: 46.2 at year 2; RCC1: 36.1 at year 2). At the end of the RCT, both RCC1 and RCC2 were switched to a mean GH dose approximately 50 mcg/kg/day similar to GHT in GHD-ANSWER patients.
Conclusions: RCT patients continued to show a sustained effect of the IGF-targeted GH treatment up to 2 years after conclusion of the randomized trial period, despite being switched from IGF-I-based dosing to a conventional dosing regimen at the end of the trial period. This indicates that the effects of the early introduction of an IGF-based regimen influences height at least 2 years after discontinuation of this approach.

Table 1. Effect of IGF-I-based dosing on ΔHSDS[a]

	Mean±SD ΔHSDS			Mean±SD ΔHSDS		
	RCT (n)	GHD-ANSWER (n)	*P* value	RCC1 (n)	RCC2 (n)	*P* value
Year 2 (end of trial)	1.7±0.8 (20)	1.0±0.6 (2491)	0.0015	1.4±0.4 (11)	2.1±1.1 (8)	0.0041
Year 3	1.9±0.7 (22)	1.3±0.7 (1680)	0.0102	1.8±0.6 (12)	2.0±0.9 (8)	0.0289
Year 4	2.2±0.7 (19)	1.5±0.8 (961)	0.0057	2.1±0.5 (9)	2.5±1.0 (7)	0.1595

[a]Determined after controlling for the effects of sex, age and baseline HSDS.

P03-37
Once-weekly, CTP-modified hGH (MOD-4023) is effective in growth hormone deficient adults: A phase II, dose and frequency finding study

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Objective: Growth Hormone (GH) replacement therapy currently requires daily injections, which may cause poor compliance, inconvenience and distress for patients. CTP-modified hGH (MOD-