A 4-Year, Open-Label, Multicenter, Randomized Trial of Genotropin® Growth Hormone in Patients with Idiopathic Short Stature: Analysis of 4-Year Data Comparing Efficacy, Efficiency, and Safety between an Individualized, Target-Driven Regimen and Standard Dosing

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Key Words
Cost effectiveness · Clinical trial · Growth hormone · Dose of growth hormone · Height prediction model · Short stature

Abstract
Background/Aims: Growth hormone (GH) treatment regimens for children with non-GH-deficient, idiopathic short stature (ISS) have not been optimized. To compare the efficacy, efficiency, and safety of an individualized, target-driven GH regimen with standard weight-based dosing after 4 years of treatment. Methods: This is a 4-year, open-label, multicenter, randomized trial comparing individualized, formula-based dosing of Genotropin® versus a widely used ISS dose of Genotropin®. Subjects were prepubertal, had a bone age of 3–10 years for males and 3–9 years for females, were naive to GH treatment, and had a height standard deviation score (Ht SDS) of –3 to –2.25, a height velocity <25th percentile for their bone age, and peak stimulated GH >10 ng/ml. After the first 2 years, the individualized-dosing group was further randomized to either 0.18 or 0.24 mg/kg/week. Results: At 4 years, subjects in all treatment regimens achieved similar average height gains of +1.3 SDS; however, the individualized dosing regimen utilized less GH to achieve an equivalent height gain. Conclusion: Individualized, formula-based GH dosing, followed by a dose reduction after 2 years, provides a more cost-effective growth improvement in patients with ISS than currently employed weight-based regimens. © 2015 S. Karger AG, Basel
Introduction

Children with idiopathic short stature (ISS) can successfully be treated with recombinant human growth hormone (GH) during childhood [1]. Previous studies of GH treatment in children with ISS – often with varied treatment paradigms – have shown significant variation in the improvement in adult height [2–5]. More recent data, using sophisticated mathematical modeling, have suggested that short-term increases in height velocity are optimized by using variable-dose treatment regimens beginning at a younger age, based upon prior growth pattern and family characteristics [4, 6]. Observations made from mathematical modeling of data from the Kabi International Growth Study (KIGS) database in children with pediatric GH deficiency [7], Turner syndrome [8], and small for gestational age [9] identified 2 important points: first, that the resultant first-year growth velocity (GV) is most strongly correlated with the dose used in the non-GH-deficient states and, second, that the second-year (and subsequent) GV is most strongly correlated to the GV in the first (or prior) year [10]. We, therefore, hypothesized that, during the first 2 years of GH therapy, a child’s growth is ‘programmed’ to a specific ‘channel’ and that, by initiating therapy with a ‘relatively high’ dose of GH, a greater height channel can be reached that can then be maintained using a lower dose.

We conducted a 4-year prospective trial of 316 children with ISS with the goal of identifying a more efficient treatment paradigm than current approaches – by inducing a more consistent catch-up growth within the first 2 years of treatment – followed by a dose reduction to maintain that height gain. We have previously reported the 2-year efficacy and safety endpoints of this trial [11], and demonstrated that both treatment groups grew to within the normal range [mean height standard deviation score (Ht SDS) –1.4, approximate mean height gain +1.0 SDS, with no difference between the 2 treatment arms in terms of height gain or the variability of the growth response]. We now describe the complete results, including the second phase of the trial, i.e. the maintenance phase, wherein 2 approximately physiological GH doses (0.18 and 0.24 mg/kg/week) were compared with a commonly used dose in the US (0.37 mg/kg/week) to identify the lowest dose necessary to maintain growth along the previously achieved height percentile. We describe the efficacy, efficiency, and safety of 3 different dosing regimens in the maintenance phase of GH treatment.

Subjects and Methods

The detailed design and subject population of this 4-year, open-label, multicenter (40 US sites) randomized trial of daily recombinant human GH (Genotropin®; Pfizer, Inc., New York, N.Y., USA) in subjects with ISS (n = 316) has been previously reported [11]. Briefly, at the trial start, subjects were randomized [2:1 ratio, stratified by age (≤7 and >7 years) and gender] to receiving either an individualized, formula-based dose (Appendix A) or a standard weight-based dose. The individualized, formula-based dose (ranging from 0.18 to 0.70 mg/kg/week) was aimed at reaching a targeted height goal of –1.3 SD (i.e. the 10th percentile) within 2 years and was followed by a decrease to approximately physiological dosing for the remaining 2 years (maintenance phase) (fig. 1). During the maintenance phase, encompassing the final 2 years of the trial, those initially receiving individualized dosing of GH were re-randomized (1:1 ratio) to 1 of 2 maintenance doses: either 0.18 or 0.24 mg/kg/week. The other group continued to receive the standard weight-based dose of 0.37 mg/kg/week for the entire 4 years in line with the dosing paradigm commonly used in the US for treatment of ISS (fig. 1). Weight-related dose adjustments were made every 4 months for all subjects.

The objectives of the 4-year analysis presented here were to evaluate treatment efficacy and efficiency after 4 years among the different dose regimens. In addition, safety evaluations were performed on all subjects.

Efficacy in the overall trial was evaluated by calculating the Ht SDS change from baseline (start of treatment) to month 48 in the standard-dose group vs. the 2 maintenance-dose groups (i.e. subjects initially randomized to the individualized dosing).

Efficacy analyses were performed on all randomized subjects who received at least 1 dose of treatment and had at least 1 post-baseline Ht SDS value, according to the subject’s treatment arm at randomization (‘as-randomized’). Estimates of the treatment differences, for both efficacy and efficiency endpoints, between the standard and maintenance doses were obtained using an analysis of covariance (ANCOVA) model with covariates for age and gender strata, and baseline Ht SDS.

We calculated the actual drug utilization (in mg) of GH at each phase of the trial and then estimated the total drug that
would be needed to achieve the predicted adult height (PAH). We then calculated drug efficiency as the milligrams of GH used per centimeter of height attained (mg/cm) at month 48, as well as the estimated efficiency (mg/cm) of height gain until the PAH was reached. The estimated efficiency of height gain at the PAH included: (1) estimation of the PAH determined by dividing the subject’s actual height by the percent of adult height attained for that bone age (BA; using the method of Bayley and Pinneau [12] on centrally read BA radiographs), and (2) estimation of the total amount of drug that would have been needed had a subject remained on treatment until adult height, using the last recorded dose in the trial, further adjusted yearly in order to account for a subject’s anticipated increase in weight; the estimate of a subject’s future weight (kg) until the PAH was calculated using Centers for Disease Control and Prevention weight-for-age reference charts.

Safety analyses were performed based on adverse event (AE) reporting and laboratory evaluations performed during the 4-year course of the trial. Safety summaries were performed on subjects with at least 1 dose of the trial drug, according to the treatment that they actually received (‘as-treated’). Safety evaluations were not assessed for statistical significance.

## Results

Of the 340 subjects screened, 316 were randomized (2:1 ratio); 202 subjects (144 males) were allocated to the individualized treatment arm, and 114 (83 males) were assigned to the standard dose arm. Treatment arms were

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### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Formula-based dose (n = 202)</th>
<th>Standard dose (n = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>boys (n = 144)</td>
<td>girls (n = 58)</td>
</tr>
<tr>
<td>Age, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 years</td>
<td>51 (35.4)</td>
<td>19 (32.8)</td>
</tr>
<tr>
<td>&gt;7 years</td>
<td>93 (64.6)</td>
<td>39 (67.2)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>117.2 ± 11.6 (83.0 to 140.4)</td>
<td>115.2 ± 9.8 (90.0 to 134.4)</td>
</tr>
<tr>
<td>Ht SDS</td>
<td>−2.54 ± 0.36 (−4.6 to −1.6)</td>
<td>−2.63 ± 0.34 (−3.9 to −2.2)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>21.9 ± 5.3 (10.7 to 36.3)</td>
<td>21.3 ± 5.1 (11.3 to 33.0)</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>n = 137</td>
<td>n = 56</td>
</tr>
<tr>
<td></td>
<td>38.4 ± 2.8 (24 to 42)</td>
<td>38.5 ± 2.5 (28 to 42)</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>n = 136</td>
<td>n = 57</td>
</tr>
<tr>
<td></td>
<td>3.0 ± 0.65 (0.7 to 4.3)</td>
<td>3.0 ± 0.55 (0.8 to 3.9)</td>
</tr>
<tr>
<td>Mother’s Ht SDS</td>
<td>n = 135</td>
<td>n = 57</td>
</tr>
<tr>
<td></td>
<td>−0.88 ± 1.05 (−4.8 to 1.4)</td>
<td>−0.94 ± 0.96 (−3.3 to 1.8)</td>
</tr>
<tr>
<td>Father’s Ht SDS</td>
<td>n = 134</td>
<td>n = 56</td>
</tr>
<tr>
<td></td>
<td>−0.64 ± 0.95 (−3.7 to 1.6)</td>
<td>−0.90 ± 1.05 (−3.7 to 1.2)</td>
</tr>
<tr>
<td>Mid-parental height, cm</td>
<td>n = 134</td>
<td>n = 56</td>
</tr>
<tr>
<td></td>
<td>171.4 ± 5.28 (155.1 to 183.2)</td>
<td>157.3 ± 5.53 (146.0 to 170.0)</td>
</tr>
<tr>
<td>BA, years</td>
<td>n = 143</td>
<td>n = 58</td>
</tr>
<tr>
<td></td>
<td>7.1 ± 2.07 (2.5 to 10.5)</td>
<td>6.9 ± 1.76 (3.0 to 10.5)</td>
</tr>
</tbody>
</table>

Values are presented as means ± SD (range) unless otherwise stated.
well balanced for age, gender, baseline Ht SDS, weight SDS, and baseline BA; baseline subject characteristics have been previously reported with the analysis of the initial phase of the trial [11] (table 1).

During the first 2 years, the individualized-dose group was treated with a median GH dose of 0.41 mg/kg/week (range 0.10–0.72). After the first 2 years, the group initially assigned to individualized GH dosing was further randomized to receive either 0.18 mg/kg/week (n = 91) or 0.24 mg/kg/week (n = 88), with the actual mean doses received being 0.18 and 0.23 mg/kg/week in the 2 subgroups, respectively. The 114 subjects in the standard-dose arm were to continue on 0.37 mg/kg/week and, in fact, their actual dose received was 0.36 mg/kg/week. Pubertal advancement was equivalent across treatment groups, with 26% of children remaining prepubertal at month 48; puberty was therefore unlikely to preferentially affect any one treatment group.

**Efficacy**

At the 2-year time point (i.e. the end of the catch-up phase), the mean height gain was 1.0 (0.5) SDS for the standard arm and 1.0 (0.5) SDS for the individualized arm. After 4 years (i.e. the end of maintenance phase and trial close), the mean height gain was 1.3 (0.7) SDS for the standard arm, 1.3 (0.6) SDS for the 0.18 mg/kg/week arm, and 1.3 (0.6) SDS for the 0.24 mg/kg/week arm (p = NS), demonstrating further equivalent modest improvement in height gain – rather than loss of the previously attained height gain – despite markedly reduced GH doses in 2 of 3 treatment arms (fig. 2a). The distribution of Ht SDS at year 4 is widest for the lowest dose – raising the possibility that 0.18 mg/kg/week may be insufficient for maintenance growth for some children. Change from baseline in IGF-I SDS was correlated with change in Ht SDS at both month 24 (correlation coefficient 0.53; 95% CI 0.44–0.62) and month 48 (correlation coefficient 0.55; 95% CI 0.45–0.63) (fig. 2b).

**Efficiency**

Over the 4-year course of this trial, the individualized dosing groups had a lower GH utilization and, therefore, had a higher efficiency of drug use (i.e. it was more cost effective) than the standard regimen because of the lower doses used in the maintenance phase along with the equivalent total height gained. During the maintenance phase of this trial, the 0.18 mg/kg/week arm used 61.1 mg/cm, compared to the standard-dose arm that used 93.7 mg/cm (p < 0.0001); drug efficiency was improved by 35% relative to the standard arm. The 0.24 mg/kg/week maintenance arm was 22% more efficient than the standard arm (73.3 vs. 93.7 mg/cm); however, this difference was not statistically significant at the 4-year point.

The predicted drug efficiency from the actual end of the trial (year 4) until the PAH was estimated to be 48% greater in the 0.18 mg/kg/week arm than in the standard arm (p < 0.0001), while in the 0.24 mg/kg/week arm it was 41% greater, but this was not statistically significant.

Overall, from baseline to the PAH, the 0.18 mg/kg/week maintenance arm was estimated to be 37% more ef-
ficient than the standard-dose arm (154.5 vs. 297.1 mg/cm, p < 0.0001), while the 0.24 mg/kg/week maintenance arm was 28% more efficient than the standard-dose arm (176.6 vs. 297.1 mg/cm, p < 0.0001).

Post hoc Analyses
In order to further describe changes in height over the 4 years, we performed several post hoc analyses. The change in PAH, relative to the mid-parental height, is a surrogate measure of height deficit that factors in changes in BA and pubertal status over time (fig. 3). By this measure, the height deficit decreased from –1.42 SDS at baseline to –0.18 SDS at 24 months in the individualized arm and from –1.29 SDS to –0.22 SDS in the standard-dose arm. At 48 months, the height deficit was –0.12, +0.004, and +0.08 SDS for the 0.18, 0.24, and 0.37 (standard dose) mg/kg/week groups, respectively. BA advanced at the same rate as chronological age in all children (fig. 4).

Safety
The heart rate, systolic and diastolic blood pressures, and body mass index changed throughout the trial in both treatment groups, as expected for the increase in age and body size of the subjects. The mean BA and sexual maturation advanced similarly in male and female subjects and across all treatment groups throughout this trial.

Serum IGF-I levels rose in all groups, with no differences among the groups at any time during this trial (see Appendix A). Throughout the trial, 85–91% of serum IGF-I values were within the normal range. Oral glucose tolerance tests, HbA1c, and homeostatic model assessment to quantify insulin resistance showed age-related changes with no difference between the treatment groups. The proportion of laboratory test abnormalities and physical examination abnormalities was similar between all of the groups and consistent with previous reports in children with ISS receiving Genotropin® [13, 14].

Fig. 3. PAH SDS – mid-parental height (MPH) SDS by age at baseline, year 2, and year 4.

Fig. 4. Change in BA over change in chronological age (CA) – by age and gender strata.
The majority of AEs were mild in severity and similar in all groups, and no deaths were observed in this trial. All-causality AEs were reported in 165 (83.3%) subjects in the individualized-dose group and 103 (87.3%) subjects in the standard-dose group. Similarly, treatment-related AEs were reported in 52 (26.3%) subjects in the individualized-dose group and 28 (23.7%) subjects in the standard-dose group. The most frequent treatment-related AEs included headaches (11.6% in the individualized-dose group vs. 8.5% in the standard-dose group) and scoliosis (6.1 vs. 6.8%). Headache and migraine [1 (0.5%) subject each] were the only severe treatment-emergent AEs reported for subjects in the individualized-dose group. No severe treatment-related treatment-emergent AEs were reported for any subject in the standard-dose group. There were, however, more subjects with serious AEs in the standard-dose group (13; 11.0%) compared to the individualized-dose group (7; 3.5%). Throughout the course of the 4-year trial, no new treatment-related safety signals emerged. Overall, safety was consistent with previous reports of children with ISS receiving treatment with Genotropin® [13, 14].

Discussion

We conducted the largest prospective, randomized, and controlled clinical trial of GH treatment in children with ISS to date. The individualized, formula-based GH dosing regimen utilized in this trial (0.18–0.7 mg/kg/week) was designed to induce catch-up growth within the first 2 years, with greater efficacy and predictability and with less variability than standard dosing of GH, followed by a maintenance phase designed for efficient use of GH. The desired change in Ht SDS was defined prospectively to facilitate the calculation of the GH dose needed to achieve the targeted result.

The results of this trial showed that use of an individualized dose that targeted height to −1.3 SDS (10th percentile) did not lead to a more consistent rapid attainment of that goal when compared to standard weight-based dosing. However, all groups reached a mean Ht SDS of −1.4 after 24 months of GH treatment and a mean Ht SDS of −1.2 after 48 months of GH treatment. Ht SDS gains (change in Ht SDS from baseline with the last observation carried forward) were +1.0 SDS at 24 months and +1.3 SDS at 48 months in all dose groups. The equivalence of the height gain across the 3 treatment arms further demonstrates that the height gain in the maintenance phase was not GH dose dependent. Puberty could have had an effect on growth; however, the pubertal effect was equivalent across the treatment arms. While not addressing the issue of whether GH was needed during the pubertal growth spurt, the effect of puberty on growth would not impact the greater utility of the reduced dose over standard weight-based dosing. The Ht SDS response in our cohort was similar to that of both the IGF-I-Based Dosing Trial of Short Children [5] and the trial by Kristrom et al. [4], which also compared an individualized dose to a standard, weight-based dose.

During the initial catch-up phase of this trial, the median GH dose utilized in the individualized-dose group was 0.41 mg/kg/week, with a wide spectrum of doses utilized (ranging from 0.10 to 0.72 mg/kg/week) as determined by the trial-specific formula and available dosing increments. The initial GH dose utilized in the treatment of a child with ISS seems to play a particularly significant role in the attempt to achieve rapid catch-up growth. Early treatment with GH at supraphysiological doses appears to produce the greatest increases in adult height [14–16]. A trial published by Wit et al. [17] suggested that the GH dose chosen for the first year of therapy has a significant impact on the adult Ht SDS, with a dose of 0.37 mg/kg/week being more effective than a dose of 0.24 mg/kg/week. Importantly, in the trial by Wit et al. [17], there was no improved growth in subjects initially treated with 0.24 mg/kg/week who had their subsequent dose increased to 0.37 mg/kg/week after the first year.

Previous reports have indicated an overall dose-dependent effect of GH on final height in children with ISS [14, 15]. However, our trial demonstrated that a reduction of the GH dose by an average of 51% (ranging to as much as 60% in some subjects) after 2 years of therapy was still able to preserve the achieved height gain as well as a standard dose of 0.37 mg/kg/week for 4 years. Demonstration of the efficacy of lower mean GH doses (0.18 and 0.24 mg/kg/week) during the maintenance phase of the treatment of patients with ISS suggests that growth during the post-catch-up phase is not GH dose dependent and, therefore, represents an important finding that differs from the traditionally held belief that patients with ISS generally require higher-than-average GH dosing due to intrinsic GH resistance [5, 16, 18]. Our finding is in agreement with that of Decker et al. [19], who studied 27 children with ISS who had their GH doses reduced by 50% after an initial 2-year catch-up phase. The authors found that ‘... serum IGF-I is no longer the major growth factor in the maintenance growth period when channel-parallel growth has been achieved.’

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In this trial, we showed that similar growth could be attained, after the catch-up phase, with 0.18, 0.24, and 0.37 mg/kg/week of GH. This is the first trial to show this degree of GH savings (efficiency). The knowledge that lower GH doses (following catch-up growth) are effective at maintaining Ht SDS in children with ISS should lead to lower overall dosing and meaningful improvements in GH drug utilization.

The new treatment paradigm described herein results in significantly more efficient drug utilization than maintaining a consistent (mg/kg) dose over the treatment lifetime; the improved drug utilization is even more pronounced when compared to the common practice of raising the (mg/kg) dose in the latter treatment years, aimed at combating growth deceleration and a shrinking treatment window, given the mass of the older – and larger – child.

GH treatment for ISS is expensive [20–22]. Moreover, pediatric endocrinologists have faced increasingly difficult challenges when trying to obtain approval from third-party payers to cover the costs of GH therapy in patients with ISS. Insurer/payer policies for GH treatment vary strikingly for conditions other than classical GH deficiency. In treating children with ISS with GH, the differences between physician recommendations and insurance coverage are often significant [23]. A new treatment paradigm that achieves significant Ht SDS improvements while lowering the drug utilization (and, therefore, the cost) is of great general medical and societal import but becomes particularly important in situations when insurer policies limit the GH dosage that can be prescribed or when the family is required to pay for the overall treatment costs due to a lack of insurance coverage.

Additional potential advantages of lowering the overall GH exposure in the treatment of ISS patients include a theoretical reduction of the risk of side effects and a lower risk of rapid acceleration of skeletal maturation [24, 25], although it should be noted that we did not observe any differences in either the safety profile or the rates of skeletal maturation or pubertal advancement between the dose groups during the 4-year course of this trial.

No new safety concerns were identified at the doses of GH employed during the 4 years of this trial, and there were no significant differences in glucose homeostasis markers or serum IGF-I levels between the 2 groups during either the initial or final 2 years of this trial. Moreover, mean BA and sexual maturation appeared to advance similarly in male and female subjects and across all treatment groups throughout this trial.

Conclusion

Our data demonstrate that the growth response to exogenous GH in children with ISS can be effectively achieved within a 2-year catch-up window, is not dose dependent following that catch-up phase, and can be achieved using significantly less GH than the current standard practice in the US. Individualized, formula-based dosing (to induce catch-up growth), followed by a dose reduction after 2 years (to maintain the achieved height gain), provides a more cost-effective growth improvement in patients with ISS than currently employed standard weight-based regimens.

Appendix A

Dosing Formula

For subjects randomized to the individualized dosing group, the initial dose of Genotropin® was determined using a formula based on the ‘early’ growth prediction model (Mearly) of Albertsson-Wikland et al. [26] and by estimating the ‘average’ dose-response curve from the literature [1–7]. The Mearly model to predict the change in Ht SDS at 2 years (ΔHt SDS2 years) involves a series of hierarchical, nested, nonlinear equations based on the following 10 variables: weight for Ht SDS at GH start, difference between paternal and maternal Ht SDS, age (years) at GH start, target Ht SDS (gender adjusted), Ht SDS 1 year before GH start, Ht SDS at GH start, ΔHt SDS during the pretreatment year, ΔHt SDS from 2 years of age to GH start, change in weight for Ht SDS from 1 year of age to GH start, and Wt SDS at birth. Exact definitions for all intermediate quantities as well as the model coefficients (k01 through k18) used to arrive at the estimate of ΔHt SDS2 years, are given in the appendix of the study by Albertsson Wikland et al. [26].

Once the predicted ΔHt SDS2 years is obtained for a given subject, the initial dose of GH is calculated by estimating the subject’s individual sensitivity by comparing their predicted response to the ‘average’ response obtained from the literature. Specifically, we approximated the dose-response curve of dose (mg/kg/week) versus ΔHt SDS2 years from 7 studies, where a dosing range of 0.19–0.70 mg/kg/week resulted in an Ht SDS change at year 2 from 0.50 to 1.50. The dose-response curve was approximated using a 3-parameter Weibull distribution with the parameters α = 1.727, β = –1.796, and γ = 2.662. Thus, given the subject’s Mearly-model-predicted ΔHt SDS2 years one can then obtain the dose needed in order to achieve the targeted Ht SDS at 2 years, defined to be –1.30 SDS, as: Dose = –(1/2.622) × ln[-1.30 – Ht SDSstart – (predicted ΔHt SDS2 years) – 0.595].

Appendix B

ISS Study Group

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Acknowledgments

We thank the subjects and their families for their participation in this study.

Disclosure Statement

The clinical trial that generated this data was funded by Pfizer, Inc. There was no honorarium, grant, or other form of payment given to anyone to produce the manuscript (note that the authors M.P.W., J.H.-H., and N.R. are employees of Pfizer and so received salary during their time working on this project).

P.T., D.R.C., and M.E.G. have received grant support from Eli Lilly, Inc., Genentech, Inc., and Pfizer, Inc. (including for this study), as well as research support from Novo Nordisk; M.E.G. has received grant support and also served on the Data Safety Monitoring Board for Ipsen. M.E.G. and L.S. have served on an Advisory Board for Merck-Serono and Advisory Boards for Pfizer, Inc. L.S. has served as a consultant/adviser to Novo Nordisk and has received speaker honoraria from Pfizer, Inc.

References


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