[RC3.2] An Ongoing Phase 2 Study of Efpegerglucagon: Promising Results on Safety and Efficacy in Subjects with Congenital Hyperinsulinism

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INTRODUCTION

Congenital hyperinsulinism (CHI) is a rare disease affecting 1 in 25,000 to 50,000 newborns, characterized by severe hypoglycemia that can lead to neurological damage or death[1]. Current treatments, which include dietary management, medications, and surgical interventions, are often limited by suboptimal efficacy and significant side effects, highlighting the urgent need for novel therapeutic approaches.

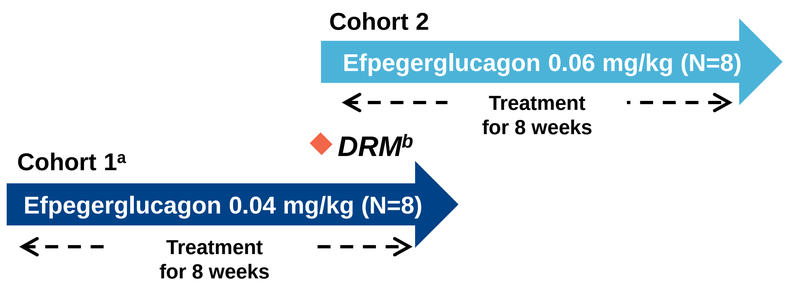
AIM

- **Primary:** To evaluate the safety, tolerability and pharmacokinetics profile of efpegerglucagon
- **Secondary:** To evaluate the reduction of weekly hypoglycemia (glucose <70 mg/dL [<3.9 mmol/L]) events by efpegerglucagon

METHOD

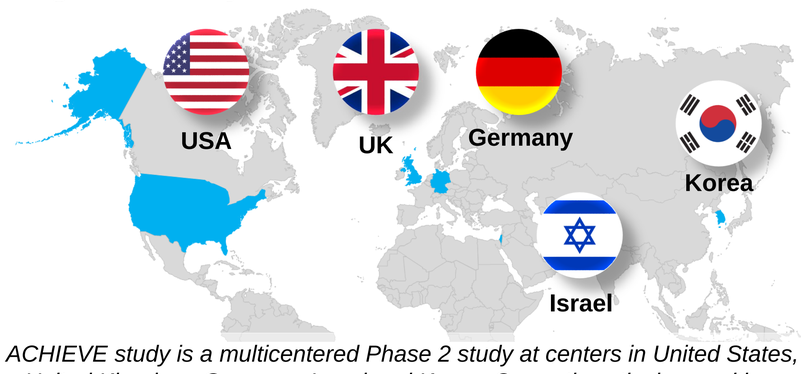
Efpegerglucagon (HM15136), a long-acting glucagon analogue, is being evaluated in a Phase 2 open-label, multicenter trial across five countries (ACHIEVE, NCT No. 04732416, EUCT No. 2024-515290-98-00). The study targets CHI patients aged two years and older with recurrent hypoglycemia (>3 episodes/week) despite standard care. The trial includes two dosing cohorts: Cohort 1 (0.04 mg/kg) and Cohort 2 (0.06 mg/kg). Each cohort consists of 8 subjects receiving weekly subcutaneous injections over an 8-week period. Enrollment for Cohort 1 (n=8, median age: 16 years, equal male-to-female ratio) has been completed, and Cohort 2 is currently ongoing.

Figure 1. Study Cohorts



a: The enrollment of subjects in Cohort 1 (N=8) will always precede enrollment in Cohort 2, in case of overlapping enrollment.
b: After the sixth subject completed the 8-week treatment period in Cohort 1, a data review meeting (DRM) was held to determine dose escalation to Cohort 2.

Figure 2. Study Centers



ACHIEVE study is a multicentered Phase 2 study at centers in United States, United Kingdom, Germany, Israel and Korea. Currently actively recruiting.

RESULTS

Table 1. Demographic Characteristics

Characteristics	Cohort 1 (N=8)
Age (years), Mean ± SD (Median)	**17.6 ± 13.8 (16.0)**
Sex, n (%)	
Male	**4 (50.0%)**
Female	**4 (50.0%)**
Baseline body weight (kg), Mean ± SD (Median)	**43.5 ± 19.5 (54.3)**
Baseline HbA1c (%), Mean ± SD (Median)	**4.7 ± 0.6 (4.9)**

SD, Standard Deviation; HbA1c, glycated hemoglobin.

Safety

- Efpegerglucagon was safe and well tolerated, with no significant changes in vital signs, physical exams, safety lab tests, or ECGs.
- Frequent Adverse Events: gastrointestinal (e.g., upper abdominal pain, diarrhea, vomiting, nausea) and metabolic (e.g., hyperglycemia, decreased appetite), mostly mild to moderate.
- Table 2 shows the number of subjects who experienced TEAEs. No events leading to discontinuation, special interest, or death.

Table 2. Overall Summary of Adverse Events

Adverse Events Category	Cohort 1 (N=8) n (%)
Any TEAE	**8 (100.0)**
CTCAE Grade[a]	
Grade 1 severity (Mild)	8 (100.0)
Grade 2 severity (Moderate)	5 (62.5)[b]
Grade 3 severity (Severe)	3 (37.5)[c]
Any study treatment related TEAE	**8 (100.0)**
Any serious TEAE	**2 (25.0)**
Any serious study treatment related TEAE	**1 (12.5)**

a: Adverse events were graded using CTCAE Version 5.0.
b: Majority of TEAEs were unrelated. Two subjects reported moderate TE AEs related to the study drug (hyperglycemia). One subject reported mod erate TEAEs related to the study drug (hyperglycemia and blood glucose f luctuation). One subject reported moderate TEAEs related to the study dr ug (hyperglycemia and increased blood ketone body).
c: Two subjects reported severe TEAEs (gastroenteritis viral and clavicle f racture) unrelated to the study drug. One subject reported a severe TEAE related to the study drug (hypoglycemia).

Pharmacokinetics (PK)

- The mean elimination half-life at Week 8 was 89.4 hours, which supports the weekly dosing interval.

Table 3. PK Parameters

Parameter (unit)	Mean(SD) observed values	
	Week 1 (N=8)	Week 8 (N=7)
C_{max} (ng/mL)	107.3 (54.0)	201.4 (127.8)
t_{max} (hour)	65.9 (35.7)	24.9 (19.8)
$t_{1/2}$ (hour)	N/A[a]	89.4 (36.2)
AUC_{0-168} (ng·h/mL)	10953.6 (5880.5)	20152.5 (7009.2)

Note: mean and SD are rounded to one decimal place.
a: due to insufficient data at the week 1 timepoint, the lambda value could not be calculated, and consequently, the half-life could not be determined.

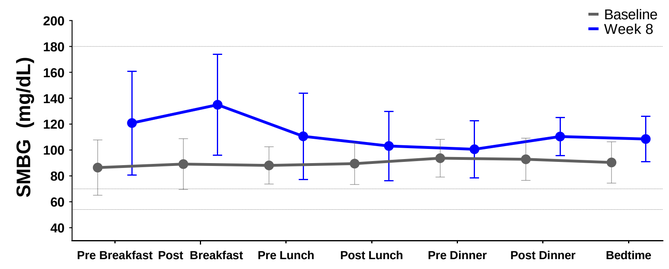
Figure 3. Efpegerglucagon Serum Concentration

* Error bars denoted SD.

Efficacy

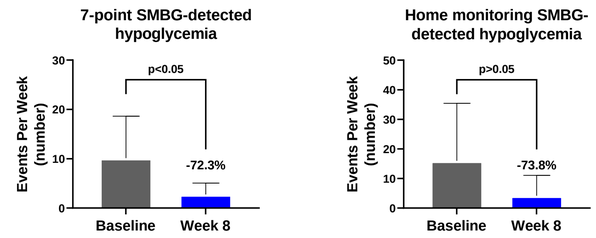
- **7-point SMBG-detected hypoglycemia**
  Level 1 or 2 hypoglycemia events (blood glucose <70 mg/dL [<3.9 mmol/L]) decreased from 10.1 (±8.5) at baseline to 2.8 (±2.3) at week 8. Notable reductions in level 2 hypoglycemia events (blood glucose <54 mg/dL [<3.0 mmol/L]) at Week 8 compared to baseline were also observed.
- **Home monitoring SMBG-detected hypoglycemia**
  Level 1 or 2 hypoglycemia events decreased from 16.0 (±19.4) at baseline to 4.2 (±6.9) at week 8.
- **Continuous glucose monitoring system(CGMS)-detected hypoglycemia**
  Notable reductions in the weekly rate of level 1 or level 2 hypoglycemia events were demonstrated.

Figure 4. 7-point SMBG Measurements



* Error bars denoted SD.

Figure 5. SMBG Detected Level 1 or Level 2 Hypoglycemia Event/Week



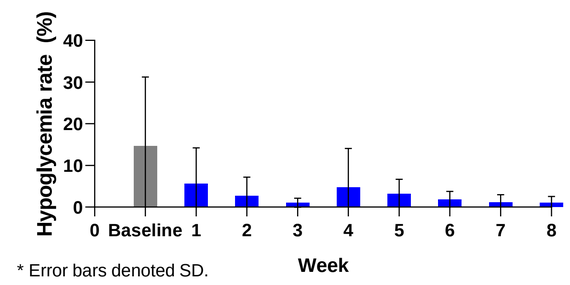
* Error bars denoted SD. Two-sided P value < 0.05 with the Wilcoxon Signed-Rank Test.

Table 4. Continuous Glucose Monitoring System(CGMS) Measures of Hypoglycemia

Measure	Mean(SD) observed values	
	Baseline (N=8)	Week 8 (N=6)
Time (min) <70 mg/dL (<3.9 mmol/L) per 24-hour period	230.75 (228.16)[a]	34.33 (19.85)[b]
Time (min) <54 mg/dL (<3.0 mmol/L) per 24-hour period	86.03 (75.10)[c]	13.75 (3.31)[d]
% time <70 mg/dL (<3.9 mmol/L) per 24-hour period	14.70 (16.52)	1.07 (1.47)
% time <54 mg/dL (<3.0 mmol/L) per 24-hour period	2.75 (3.29)	0.18 (0.26)

a: n=7. b: n=4. c: n=6. d: n=3.
Note: Baseline: daily total time spent in hypoglycemia (<70 mg/dL [<3.9 mmol/L] or <54 mg/dL [<3.0 mmol/L]) averaged across quantifiable days during Day -7 to Day -1. Week 8: daily total time spent in hypoglycemia (<70 mg/dL [<3.9 mmol/L] or <54 mg/dL [<3.0 mmol/L]) averaged across quantifiable days Week 8.

Figure 6. Time in Level 1 or Level 2 Hypoglycemia by CGMS (%)



* Error bars denoted SD.

CONCLUSIONS

Efpegerglucagon demonstrated a favorable safety profile and clinically meaningful efficacy. After eight weeks of treatment, CHI patients experienced significant reductions in hypoglycemia events. These findings emphasize its therapeutic potential as a safe and effective treatment for CHI and support the continued enrollment of Cohort 2.

REFERENCES

1) Banerjee I et al., Congenital hyperinsulinism in infancy and childhood: challenged, unmet needs and the perspective of patients and families. Orphanet Journal of Rare Disease, 2022, 17 (61)

ACKNOWLEDGEMENT

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FOR MORE INFORMATION

Investigators or CHI patients who want to learn more about participant, please visit the study website at
ACHIEVE.study

CONFLICTS OF INTEREST

- Antonia Dastamani, Susann Empting, Mala Puri, EunJi Gwak, Seohyun Kang, JinHee Byeon, Moon Hee Lee: The authors are participating in industry-sponsored clinical trials funded by Hanmi Pharmaceutical Co., Ltd.
- Indraneel Banerjee: The author discloses the following conflicts of interest: participation in industry-sponsored clinical trials funded by Zealand Pharma, Rezolute, and Hanmi Pharmaceutical Co., Ltd.; has received research grants from the University of Manchester, Manchester BRC, and NIHR; and currently serves as the Chair of the ESPE Communications Committee and as an Associate Editor for Frontiers in Endocrinology.
- Diva D. Leon-Crutchlow: The author discloses the following conflicts of interest: consulting for AmideBio, Spruce Biosciences, Zealand Pharma, Twist Bioscience, Rhythm Pharmaceuticals, Eiger Biopharmaceuticals, and Rezolute; participation in industry-sponsored clinical trials funded by Zealand Pharma, Rezolute, Hanmi Pharmaceutical Co., Ltd., Eiger Pharma, and Ultragenyx; and receipt of investigator-initiated research support from Twist Bioscience.