Safety and efficacy of efpegerglucagon in patients with congenital hyperinsulinism: interim results from a phase 2 study

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INTRODUCTION

Congenital hyperinsulinism (CHI) is a rare disease affecting 1 in 25,000 to 50,000 newborns that requires emergent treatment of recurrent hypoglycemia to prevent neurological sequelae[1]. There is a high unmet need for novel treatments due to the limited effectiveness and adverse effects associated with the current standard of care medications, namely diazoxide and somatostatin analogues.

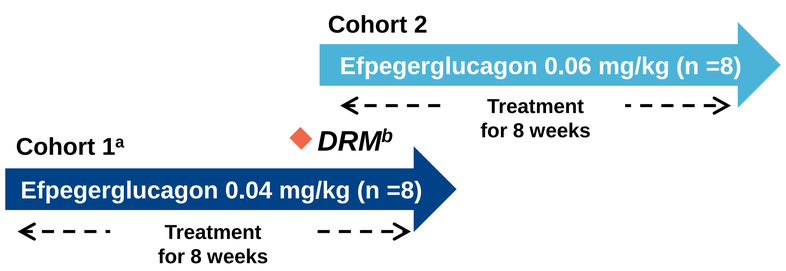
AIM

- **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

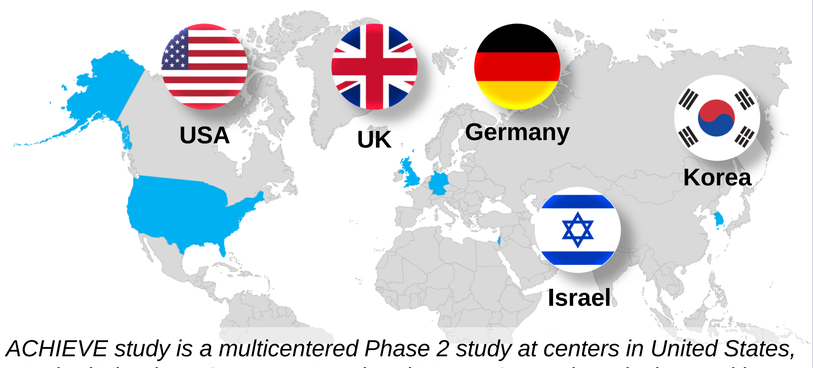
Efpegerglucagon (HM15136) is a novel long-acting glucagon analogue conjugated with a human IgG Fc fragment to provide a longer half-life than traditional glucagon. Currently, an open-label phase 2 trial is ongoing to assess the therapeutic potential of efpegerglucagon in CHI patients aged two years and older who experience recurrent hypoglycemia events (> 3 episodes/week) while on standard of care (SoC) treatment (ACHIEVE, NCT No. 04732416, EUCT No. 2024-515290-98-00). In this study, eight patients receive weekly doses of subcutaneous efpegerglucagon for eight weeks at each of the two dosing levels (Figure 1).

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 completes the 8-week treatment period in Cohort 1, a data review meeting will be 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=6)
Age (years), Mean ± SD	21.2 ± 14.3
Sex, n (%)	
Male	2 (33.3%)
Female	4 (66.7%)
Baseline body weight (kg), Mean ± SD	50.8 ± 61.4
Baseline glycated hemoglobin (HbA1c), Mean ± SD	4.7 ± 0.6
Abbreviations: F = Female; M = Male; SD=Standard Deviation.	

Safety

- Efpegerglucagon was safe and well tolerated, with no significant changes in vital signs, physical examinations, safety laboratory tests, or electrocardiograms.
- The most common adverse event was gastrointestinal disorders such as upper abdominal pain and diarrhea.
- Most of the adverse events were mild and moderate in severity.
- There were no adverse events leading to discontinuation of study treatment, adverse events of special interest, or death.

Table 2. Overall Summary of Adverse Events

Adverse Events Category	Cohort 1 (N=6) n (%)
Any TEAE	**6 (100.0)**
CTCAE Grade[a]	
Grade 1 severity (Mild)	6 (100.0)
Grade 2 severity (Moderate)	3 (50.0)[b]
Grade 3 severity (Severe)	3 (50.0)[c]
Any study treatment related TEAE	**6 (100.0)**
Any serious TEAE	**2 (33.3)**
Any serious study treatment related TEAE	**1 (16.7)**

a: Adverse events were assigned severity grade using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
b: The majority of TEAEs were considered unrelated to the study drug. One subject reported moderate severity TEAE that was considered related to the study drug (hyperglycaemia). One subject reported moderate severity TEAE that was considered related to the study drug (hyperglycaemia and blood glucose fluctuation)
c: One subject reported a severe TEAE that was considered unrelated to the study drug (viral gastroenteritis). One subject reported a severe TEAE that was considered unrelated to the study drug (clavicle fracture). One subject reported a severe TEAE that was considered related to the study drug (hypoglycemia).

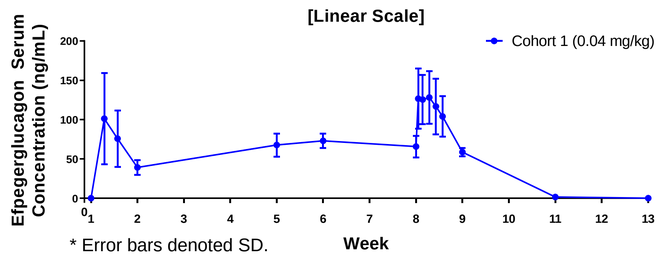
Pharmacokinetics (PK)

- The mean elimination half-life at Week 8 was 146 hours, which supports the weekly dosing interval.

Table 3. PK parameters

Parameter (unit)	Mean(SD) observed values	
	Week 1 N=6	Week 8 N=5
C_{max} (ng/mL)	103.6 (60.1)	142.0 (44.7)
t_{max} (hour)	76.0 (48.0)	30.7 (19.9)
$t_{1/2}$ (hour)	86.9 (1199.2)	146.0 (127.0)
AUC_{0-168} (ng·h/mL)	12714.1 (5350.8)	17755.7 (4482.5)
Note: mean and SD are rounded to one decimal place.		

Figure 3. Efpegerglucagon Serum Concentration

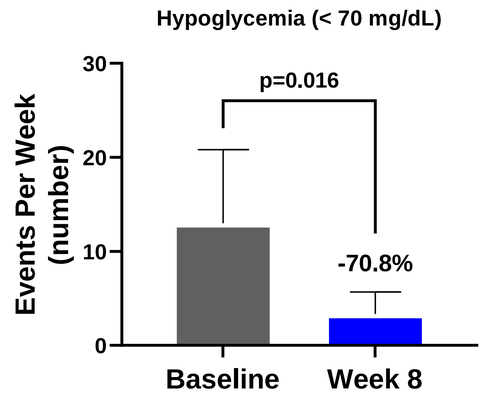


* Error bars denoted SD.

Pharmacodynamics (PD)

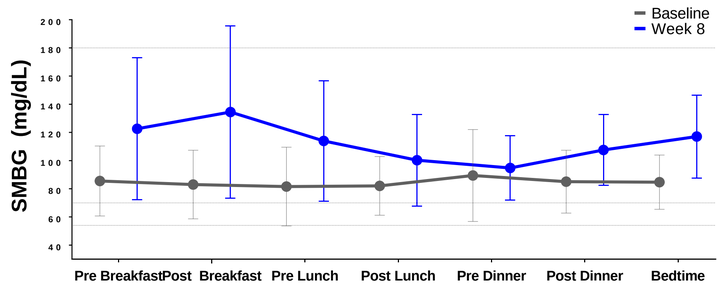
- The mean number of weekly hypoglycemia events (blood glucose < 70 mg/dL [<3.9 mmol/L]) as measured by 7-point self-monitored blood glucose (SMBG) was 3.8 (± 2.3, standard deviation) during Week 8 compared to 13.0 (± 7.8) at baseline.

Figure 4. 7-point SMBG Measures of Hypoglycemia



* Error bars denoted SD.

Figure 5. 7-point SMBG Measurements

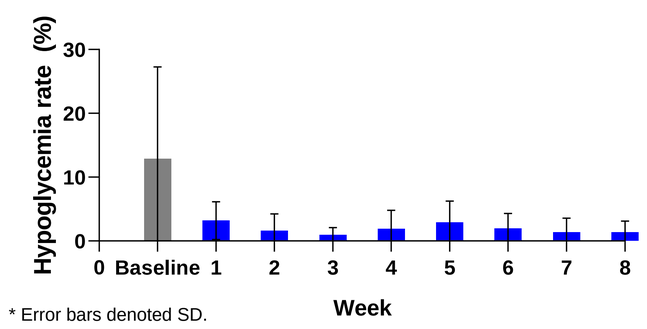


* Error bars denoted SD.

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

Measure	Mean(SD) observed values	
	Baseline N=6	Week 8 N=6
Time (min) <70 mg/dL (<3.9 mmol/L) per 24-hour period	181.85 (205.86)	39.44 (20.84)
Time (min) <54 mg/dL (<3.0 mmol/L) per 24-hour period	76.03 (79.38)[a]	13.75 (3.31)[b]
% time <70 mg/dL (<3.9 mmol/L) per 24-hour period	12.91 (14.35)	1.34 (1.77)[c]
% time <54 mg/dL (<3.0 mmol/L) per 24-hour period	2.23 (2.51)	0.27 (0.29)[c]
a: n=5. b: n=3. c: n=4. 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 Hypoglycemia (<70 mg/dL) by CGMS (%)



* Error bars denoted SD.

CONCLUSIONS

After eight weeks of treatment with efpegerglucagon, patients with CHI demonstrated clinically significant reductions in hypoglycemia events. These findings, combined with favorable safety and tolerability profiles, strongly suggest its therapeutic potential as a safe and effective therapy for CHI patients.

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