Effect of Human pro-Islet Peptide 2B on β-cell Function in Metformin-Treated Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Study

Watkins E[1], Morrow L[1], Krentz AJ[1], Feig PU[1], Upham L[2], Reiser HJ[2], Hompesch M[1]

1. Profil Institute for Clinical Research, Chula Vista, CA, USA; 2. CureDM, Inc. Wilmington, DE, USA

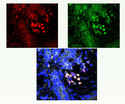
ABSTRACT

Human pro-Islet Peptide (HIP2B) stimulates differentiation of pancreatic progenitor cells into new islet structures. In a single center, phase 1b randomized, double-blind, parallel group, placebo-controlled study the effects of 49 days of treatment with HIP2B were examined in adults with metformin-treated type 2 diabetes. Subjects received HIP2B 400mg (n=14 mean [+SD] age 53 + 6 y; BMI 32.8 + 5.1 kg/m^2) or 600 mg (n=14 age 52 + 8 y; BMI 32.4 + 5.2 kg/m^2) or placebo (n=10; age 56 + 7 y; BMI 31.8 + 5.3 kg/m^2) in a ratio of 3:3:2 respectively as twice-daily (BID, every 12 h ±1 h) subcutaneous injections. Metabolic evaluations were performed during seven in-house periods. Of 38 subjects who were enrolled 30 completed the study. PK: dose-related increases in C_{max} and AUC were observed for HIP2B with no significant difference between the two doses. Changes in prehepatic insulin secretion rates (pmol/kg/min) Placebo: -60.5 +/- 61.25; HIP2B 400 mg: 60.63 +/- 37.17; 600mg: 55.13 +/- 24.31; pooled HIP2B: 58 +/- 22.13 (p=0.031) were observed. Injection site reactions being the most common AE, were of mild to moderate intensity. No clinically significant changes in clinical laboratory values, vital signs or ECGs were observed thus achieving the primary endpoint. In conclusion, treatment with HIP2B was associated with trends towards increased insulin secretion with a statistically significant increase in pre-hepatic insulin secretion rates from baseline to Day 46 in the pooled HIP2B treatment groups. The results support additional studies of HIP2B in type 2 diabetes.

BACKGROUND

Human Pro-Islet Peptide (HIP2B) is a 14 amino acid peptide derived from the Reg gene that is known to stimulate the natural process of islet neogenesis. HIP2B is being developed for the treatment of type 1 and type 2 diabetes mellitus.

- HIP2B stimulates existing progenitor cells in the pancreas to differentiate into new healthy islet structures in order to:
  - supplement endocrine function and alleviate stress on existing islets in T2DM, or
  - re-establish function in the absence functional islets in T1DM, in combination with an immune tolerance or immune suppression treatment.[1]
- HIP2B binds to EXTL3, the transmembrane Receptor found on progenitor cells and triggers upregulation of known transcription factors that lead to islet neogenesis.[2]



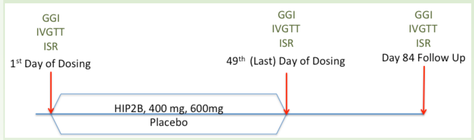
Biotinylated-HIP2B = green (FITC)
EXTL3 positive cells = red (Cy3);
Co-localization = orange

- Lack of first-phase insulin secretion is usually profound when T2DM is established and fasting hyperglycemia is present as a function of reduced islet number[3] and/or reduced β-cells.[4,5]
- A key aspect of HIP2B is its ability to stimulate islet neogenesis faster than the attrition rate making T2DM is a logical disease target.

METHODS

Methodology:
This was a phase 1b, single center, randomized, double-blind, parallel group, placebo-controlled study of the effect of 49 days of treatment with repeated subcutaneous (SC) doses of HIP2B on measures of islet β-cell function in adults with T2DM.

- Double Blind, Placebo, Controlled Phase 1b
- Total of 38 Subjects
- 3:3:2 (600mg:400mg:placebo)
- BID, every 12 hours ±1 hour SC
- Seven In-house Visits for GGI[6], IVGTT[7], ISR[8,9]



	HIP2B		
	400 mg (N=14)	600 mg (N=14)	Placebo (N=10)
Age			
Mean	53	52	56
Median	54	53	56
Min , Max	38 , 62	37 , 64	44 , 65
Gender			
Male	10 (71%)	6 (43%)	6 (60%)
Female	4 (29%)	8 (57%)	4 (40%)
Race			
Asian	1 (7%)	0	0
Black or African American	0	2 (14%)	0
White	13 (93%)	12 (86%)	10 (100%)
Ethnicity			
Hispanic/Latino	12 (86%)	10 (71%0	8 (80%)
Non-Hispanic/Latino	2 (14%)	4 (29%)	2 (20%)
Weight (kg)			
Mean	93.3	88.6	86.7
Median	92.1	89.0	78.2
Min , Max	60.4 , 132..3	63.4 , 124.4	68.8 , 123.4
BMI (kg/m^2)			
Mean	32.8	32.4	31.8
Median	31.1	31.8	30.5
Min , Max	26.1 , 40.9	24.5 , 40.0	24.1 , 40.9
Fasting Plasma Glucose (mg/dL)			
Mean	140	132	147
Median	136	130	138
Min , Max	105 , 200	104 , 160	109 , 210
HbA1c (%)			
Mean	7.6	7.4	7.9
Median	7.3	7.2	7.9
Min , Max	6.6 , 9.5	6.5 , 9.4	6.6 , 9.5
Metformin dose at entry			
Mean	1436	1568	1460
Median	1500	1850	1600
Min , Max	500 , 2550	500 , 2550	500 , 2550

RESULTS: Safety Evaluation

Twice-daily subcutaneous administration of HIP2B at 200 mg BID (400 mg daily) and 300 mg BID (600 mg daily) for 49 days is generally safe and well tolerated.

- The types of reported AEs were generally similar between both doses of HIP2B and placebo and did not result in patient dropouts.
- no clinically significant changes in the clinical laboratory parameters (chemistry, hematology, urinalysis) during the study.
- no clinically significant changes in ECGs or vital signs.

RESULTS: Pharmacodynamic Effects

Change from Baseline to Day 46 in Incremental AUC Insulin-GGI (±SE)

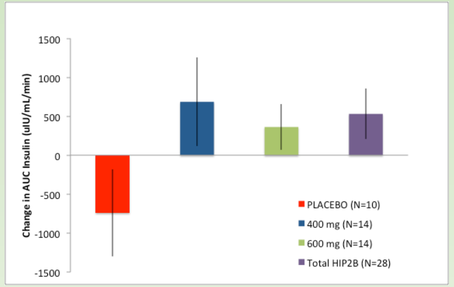


Figure 1: Change from Baseline to Day 46 in Incremental AUC Insulin-GGI (±SE) Total HIP2B = combined HIP2B treatment groups (i.e., HIP2B 400 mg + 600 mg) 400mg group p=0.056, 600mg group p=0.146, Total HIP2B p=0.058.

Change from Baseline to Day 46 in Pre-Hepatic Insulin Secretion Rate-GGI (±SE)

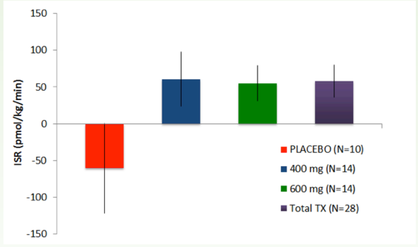


Figure 2: Change from Baseline to Day 46 in Pre-Hepatic Insulin Secretion Rate-GGI (±SE) ISR = insulin secretion rate, Total TX = combined HIP2B treatment groups (i.e., HIP2B 400 mg + 600 mg); 400mg group p=0.048, 600mg group p=0.061, Total HIP2B p=0.031.

Change in Slope of Insulin Secretion during GGI

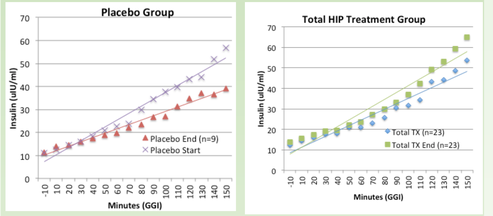


Figure 3: Improvements in insulin secretion in HIP2B group during Graded Glucose Infusion compared to placebo from start to end of study.

Change in Insulin Secretion Rate in response to IVGTT.

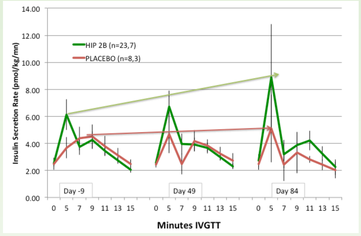


Figure 4: Change in Insulin Secretion Rate in response to IVGTT.

Changes in Hemoglobin A1c

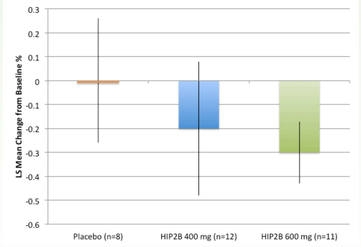


Figure 5: Least squares mean change in HbA1c from baseline to day 49 treatment with Placebo, HIP2B doses of 400mg, and HIP2B 600mg. p=NS.

CONCLUSION AND DISCUSSION

As the primary objective, results indicated that twice daily subcutaneous injections of HIP2B at 400 mg and 600 mg for 49 days were:

- well tolerated in subjects with T2DM on metformin, with
- no clinically significant changes in clinical laboratory values, ECGs or vital signs during the study, and
- no deaths or withdrawals due to AEs.

Despite the small sample size, compared to treatment with placebo, treatment with HIP2B resulted in:

- improvements in mean insulin concentrations measured by GGI from baseline to Day 46 that trended toward significance,
- mean change in pre-hepatic insulin secretion rate from baseline to Day 46 was **statistically significant** in the combined HIP2B treatment groups compared to placebo,
- improvements in mean insulin concentrations as measured by GGI and IVGTT, including some that seemed to persist during the post-treatment period.

Improvements in insulin secretion levels, and improvements in **control** of insulin secretion under glucose challenge, is the benefit of islet neogenesis as a mechanism, which lead to improvement in HbA1c.

We propose that a longer, larger definitive Phase II study will elucidate these effects of HIP2B as an important new treatment option for Type 2 Diabetes.

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CONTACT

Elaine Watkins, DO, MSPH
Profil™ Institute for Clinical Research
855 3rd Avenue, Suite 4400
Chula Vista, CA 91911 U.S.A.
(p): (619) 409-1264
elaine.watkins@profilinstitute.com

Loraine V. Upham
CureDM, Inc.
1201 Market St. Suite 701
Wilmington, DE 19801
(p): 505-515-1947
Lori@CureDM.com