Velaglucerase alfa as therapy for Gaucher disease

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Disclosure

Deborah Elstein has no current conflicts of interest; served as consultant to Shire HGT during seminal trials
Gene-Activated® GCB (GA-GCB)

A. Protein coding DNA sequences (gene) in human cell

B. Add new regulatory DNA sequences to function as an "on" switch

C. The new regulatory DNA sequences bypass the "off" switch, activating the gene

D. Large quantities of the therapeutic protein are produced by the human cell
Evolution of Protein Production

Conventional Recombinant DNA Approach

TKT’s Gene-Activation Approach
Gene-Activated GCB (velaglucerase alfa)

- GA-GCB has terminal mannose residues which target the enzyme to macrophages, the target cells in Gaucher disease
- Primary amino acid sequence of GA-GCB is identical to the human enzyme (and hence also to alglucerase)
- GA-GCB is produced in a human cell line
  - Imiglucerase, Taliglucerase alfa and Abcertin (ISU302) have a 1 amino acid difference relative to wild type sequence
  - Imiglucerase and Abcertin are produced in CHO cells and taliglucerase alfa in plant cells
Potential Advantage of Wild Type Glucocerebrosidase

pH-Dependent Activity of Imiglucerase, rhWT and rhN370S Glucocerebrosidase

<table>
<thead>
<tr>
<th>Recombinant Enzyme</th>
<th>pH</th>
<th>Activity (U/mg)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imiglucerase</td>
<td>5.3</td>
<td>9.1 ± 0.4</td>
</tr>
<tr>
<td>Imiglucerase</td>
<td>7.0</td>
<td>4.0 ± 0.3</td>
</tr>
<tr>
<td>WT</td>
<td>5.3</td>
<td>15.5 ± 0.5</td>
</tr>
<tr>
<td>WT</td>
<td>7.0</td>
<td>8.1 ± 0.4</td>
</tr>
<tr>
<td>N370S</td>
<td>5.3</td>
<td>3.0 ± 0.3</td>
</tr>
<tr>
<td>N370S</td>
<td>7.0</td>
<td>1.6 ± 0.2</td>
</tr>
</tbody>
</table>

*U = µMol of 4-methylumbelliferone released per minute

Internalization into macrophages: velaglucerase alfa versus imiglucerase

Velaglucerase alfa: Pre-clinical development

- **Bio-distribution of GA-GCB**
  - Immuno-histochemistry

- **Pharmacokinetics of GA-GCB**
  - Rats, dogs, & monkeys

- **Toxicology summary**
  - Acute and long-term studies in rats & monkeys
# Velaglucerase alfa: Clinical Trial Program

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Phase</th>
<th>Duration</th>
<th>Patients (enrolled or randomized)</th>
<th>Dose group (EOW)</th>
<th>Design</th>
<th>Splenectomy Status at BL</th>
</tr>
</thead>
<tbody>
<tr>
<td>TKT025</td>
<td>I/II</td>
<td>9 M</td>
<td>Naïve, adult (N=12)</td>
<td>60 U/kg</td>
<td>Open label</td>
<td>No</td>
</tr>
<tr>
<td>TKT032</td>
<td>III</td>
<td>12 M</td>
<td>Naïve, ≥2 years old (N=25)</td>
<td>45 or 60 U/kg</td>
<td>Double blind, 1:1 randomized</td>
<td>No</td>
</tr>
<tr>
<td>HGT-GCB-039</td>
<td>III</td>
<td>9 M</td>
<td>Naïve, ≥2 years old (N=35)</td>
<td>60 U/kg velaglucerase alfa or imiglucerase</td>
<td>Double blind, 1:1 randomized</td>
<td>Yes or No</td>
</tr>
<tr>
<td>TKT034</td>
<td>II/III</td>
<td>12 M</td>
<td>Transition, ≥2 years old (N=41)</td>
<td>15-60 U/kg</td>
<td>Open label</td>
<td>Yes or No</td>
</tr>
<tr>
<td>TKT025EXT</td>
<td>I/II EXT</td>
<td>7 years</td>
<td>(N=10) from TKT025</td>
<td>30-60 U/kg</td>
<td>Open label</td>
<td>No</td>
</tr>
<tr>
<td>HGT-GCB-044</td>
<td>III EXT</td>
<td>Ongoing</td>
<td>(N=95) from TKT032, TKT034 and HGT-GCB-039</td>
<td>15-60 U/kg</td>
<td>Open label</td>
<td>Yes or No</td>
</tr>
<tr>
<td>HGT-GCB-058</td>
<td>EAP</td>
<td>≤65 Wks</td>
<td>Switch, Naïve (N=211)</td>
<td>15-60 U/kg</td>
<td>Open label</td>
<td>Yes or No</td>
</tr>
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</table>
TKT 025: THE DREAM TEAM in a single center Phase I/II seminal trial and extension

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male : Female</td>
<td>5 (42%) : 7 (58%)</td>
</tr>
<tr>
<td>Ashkenazi Jewish : Other</td>
<td>8 (67%) : 4 (33%)</td>
</tr>
<tr>
<td>Mean age (years) ±SD (range)</td>
<td>41.7±17.3 (19–70)</td>
</tr>
<tr>
<td>Mean weight (kg) ±SD (range)</td>
<td>59.6 ± 9.1 (50-73)</td>
</tr>
<tr>
<td>Mean height (cm) ±SD (range)</td>
<td>169.4±8.0 (160-184)</td>
</tr>
<tr>
<td>N370S/N370S : N370S/other</td>
<td>6 (50%) : 6 (50%)</td>
</tr>
<tr>
<td>Osteonecrosis (hip joint)</td>
<td>2 (16.7%)</td>
</tr>
</tbody>
</table>
TKT 025 Phase I/II: Conclusions (9 months)

- IV infusion of 60 U/kg every other week well-tolerated
- No hypersensitivity reactions
- No anti-velaglucerase alfa antibodies
- Mean increase hemoglobin value 2.24 g/dL (1° endpoint)
- Mean increase platelet counts: 67.6%
- Mean reduction liver volume (MRI): 18.2%
- Mean reduction spleen volume (MRI): 45.9%
- Reduction in biomarkers chitotriosidase & CCL18
- Allowed initiation of Phase III studies
Eligibility Criteria for TKT 025EXT Enrollment and Dosing

**TKT025**
- Enrollment
- Diagnosis of type 1 GD
- GD-related anemia
- Thrombocytopenia
- Age ≥18 years
- Intact spleen
- No Gaucher disease-specific treatment in preceding 12 months

**TKT025**
- 9-month trial
- 60 U/kg EOW velaglucerase alfa, IV infusion

**TKT025EXT**
- Enrollment
- Completed TKT025
- 60→45→30 U/kg EOW velaglucerase alfa, IV infusion

TKT025EXT was completed in December 2011.
The maximum duration velaglucerase alfa = 79.5 months.
In TKT025EXT, stepwise dose reduction was implemented after 3 months if patients met at least 2 of 4 Therapeutic Goals (1-year goals for hemoglobin / platelet counts / spleen volume / liver volume).
Change from Baseline statistically significant at 9 months (P<0.003) and 48 months (P<0.004) for each parameter.
Percent patients achieving 4 clinical Therapeutic Goals

Anemia & thrombocytopenia at 9 months

Hepatomegaly & splenomegaly at 6 months

Time to Therapeutic Goal response with velaglucerase alfa

Anemia may be a risk factor for osteonecrosis in Gaucher disease (Khan et al, 2012)
Early achievement and maintenance of clinical Therapeutic Goals despite dose reduction

- Mean dose & percentage patients achieving all therapeutic goals
- 4 goals until 36 months; 5 goals including BMD thereafter

Significant and continuous improvement in bone mineral density among type 1 Gaucher disease patients treated with velaglucerase alfa: 69-month experience, including dose reduction

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\textsuperscript{d} Metabolic and Clinical Genetic Department, Mother and Child Health Care Institute, Belgrade, Serbia
\textsuperscript{e} "Sf Ioan" Clinical and Emergency Hospital, Bucharest, Romania
BMD Status (based on T-scores) at Baseline and 69 Months of velaglucerase alfa without bisphosphonates

- All 4 patients on bisphosphonates had no change in WHO Category
- Low BMD at LS may be a risk factor for fractures in Gaucher disease (Khan et al, 2012)
Conclusions: Improvement in BMD with velaglucerase

- In patients with baseline osteopenia/osteoporosis (and osteonecrosis) treated with velaglucerase alfa, BMD improved in both lumbar spine (Month 24) and femoral neck (Month 36)

- Improvement in bone pathology was not dependent upon continuous high-dose therapy (patients were dose-reduced to 30u/kg/EOW)
Impact of velaglucerase alfa on Bone Marrow Burden (BMB) score

- Improvements (2 point reductions) began at 9 months in some patients
- Continual improvements in BMB scores at LS & FN with most achieving normal values at LS and at least 2 point reduction in others
- Improvements in BMB parallel changes in bone density
- BMB data was evaluable earlier than other radiological indices (but later than hematology/viscera)
TKT 032: Randomized, Double-Blind, Global, Phase III Study of treatment-naïve patients at two doses (45 and 60 units/kg/EOW) 12 months

Ari Zimran¹, MD; Derlis Emilio Gonzalez Rodriguez² MD; Elena A. Lukina³, MD; Marie-Françoise Ben Dridi, ⁴ MD; Isaac Kisinovsky ⁵, MD; Eric Crombez ⁶, MD and Kiran Bhirangi ⁶, MD.

¹Shaare Zedek Medical Center, Jerusalem, Israel; ²Sanatorio Español, Asunción, Paraguay; ³National Research Center for Haematology, Moscow, Russia; ⁴La Rabta Hospital, Tunis, Tunisia; ⁵Your Health S.A., Buenos Aires, Argentina; ⁶Shire Human Genetic Therapies, Cambridge, USA
TKT032 Clinical Trial: 12 month results

Mean % change (±SEM) from Baseline: hemoglobin & platelet counts

Mean % change (±SEM) from Baseline: spleen and liver volumes

- Hemoglobin concentration (change from Baseline, %)
- Platelet count (change from Baseline, %)
- Spleen volume (change from Baseline, %)
- Liver volume (change from Baseline, %)

- velaglucerase alfa 45 U/kg (n=13)
- velaglucerase alfa 60 U/kg (n=12)
TKT 032: Results after **2 years** velaglucerase alfa

- Clinically significant changes from baseline regardless of dosage in all parameters
- Statistically significant changes from baseline in hemoglobin, platelet counts, and spleen volume
- Velaglucerase alfa was well tolerated; no drug-related SAEs
- 1 patient developed antibodies to velaglucerase alfa
- No patient discontinued the study early
Velaglucerase Alfa in Gaucher Disease Type 1 Patients switching from Imiglucerase at same dose: TKT-034 and 2 year extension results
Multicenter, 12 month Phase III Clinical Trial


Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, USA; 2University College London, London, UK; 3Shaare Zedek Medical Center and Hebrew University-Hadassah Medical School, Jerusalem, Israel; 4Children’s Mercy Hospitals and Clinics, Kansas City, MO, USA; 5Children’s Memorial Hospital, Chicago, IL, USA; 6Children’s Hospital Oakland, Oakland, CA, USA; 7Children’s Hospital of Wisconsin, Milwaukee, WI, USA; 8Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER) and Hospital Universitario Miguel Servet, Zaragoza, Spain; 9Children’s Hospitals and Clinics of Minnesota, Minneapolis, MN, USA; 10Gyeongsang National University Hospital, Jinju, Republic of Korea; 11Shire Human Genetic Therapies, Inc., Lexington, MA, USA
Changes in hemoglobin, platelets, organ volumes, and biomarkers in switch-over patients on TKT 034 trial for 24 months

**FIGURE 2.** Temporal changes from Baseline in haemoglobin concentration (n=38)

**FIGURE 3.** Temporal changes from Baseline in platelet count (n=30)

**FIGURE 4.** Temporal changes from Baseline in organ volumes

**FIGURE 5.** Temporal changes from Baseline in plasma biomarkers

Pre-specified clinically significant limits: ±1 g/dL.
TKT 034: Conclusions up to 2 years

- **1 patient had hypersensitivity reaction** at first infusion and withdrew consent

- **No patient developed anti-velaglucerase alfa antibodies**, including 3 patients who were positive for anti-imiglucerase antibody at baseline
  - 1 patient had cross reactive antibodies to velaglucerase alfa and imiglucerase throughout the study

- Switch to velaglucerase alfa was generally **well tolerated**

- There were **no differences in efficacy parameters between baseline** (i.e., switch from imiglucerase) and after 12 months of velaglucerase alfa
A multicenter, randomized, double-blind, parallel-group, non-inferiority, phase III study of velaglucerase alfa enzyme replacement therapy compared with imiglucerase in patients with type 1 Gaucher disease (HGT-HCG-039).

Marie-Françoise Ben Dridi, MD;1 Derlis E. Gonzalez, MD;2 Ari Zimran, MD;3 Madhulika Kabra, MD;4 Elena A. Lukina, MD;5 Pilar Giraldo, MD;6 Isaac Kisinovsky, MD7 Ashish Bavdekar, MD,8 Hadhami Ben Turkia, MD;1 Nan Wang, MS;9 Eric Crombez, MD;9 Kiran Bhirangi, MD;9 and Atul Mehta, MD10

1La Rabta Hospital, Tunis, Tunisia; 2Sanatorio Español, Asunción, Paraguay; 3Shaare Zedek Medical Center, Jerusalem, Israel; 4All India Institute of Medical Sciences, New Delhi, India; 5National Research Center for Haematology, Moscow, Russia; 6Hospital Universitario Miguel Servet, Zaragoza, Spain; 7Your Health S. A., Buenos Aires, Argentina; 8KEM Hospital Research Centre, Pune, India; 9Shire Human Genetic Therapies, Cambridge, MA, USA; 10Royal Free Hospital, London, UK
HGT-GCB-039: Improvement in all clinical parameters after switch: 9 month imiglucerase, then velaglucerase (60u/kg/EOW)
HGT-GCB-039/044: 24 months
Mean change Lumbar Spine BMD z-scores
(all patients and excluding patients receiving bisphosphonates)
HGT-GCB-039: Conclusions

- After 9 months Cerezyme, the switch to velaglucerase alfa was well-tolerated
- Rates of drug- and infusion-related AEs decreased after switch to velaglucerase alfa
- No patient developed anti-vela antibodies
- Continued clinical and statistical improvements in Gaucher-specific parameters & biomarkers after switch to velaglucerase alfa
Pooled TKT032 & HGT-GCB 039 and extension HGT-GCB-044: Achievement of therapeutic goals at 2 years (60u/kg/EOW)
Pooled TKT032 & HGT-GCB 039 and extension HGT-GCB-044: Improvement in Bone Density, LS and FN at 2 years (60u/kg/EOW)

- Comparable to TKT 025EXT results (both no bisphosphonates)
- Low Lumbar Spine BMD may be a risk factor for pathological fractures at both spine and femur (Khan et al, 2012)
Booster-effect with velaglucerase alfa in patients with Gaucher disease switched from long-term imiglucerase therapy: Early Access Program results from Jerusalem

Deborah Elstein a,*, Gheona Altarescu b, Hannah Maayan a, Mici Phillips a, Aya Abrahamov a, Irith Hadas-Halpern c, Maayan Tiomkin a, Ari Zimran a

a Gaucher Clinic, Shaare Zedek Medical Center, the Hebrew University and Hadassah Medical School, Jerusalem, Israel
b Genetics Unit, Shaare Zedek Medical Center, the Hebrew University and Hadassah Medical School, Jerusalem, Israel
c Department of Diagnostic Radiology, Shaare Zedek Medical Center, the Hebrew University and Hadassah Medical School, Jerusalem, Israel
SZ Early Access Program results: 19 switch-over patients

Elstein et al BCMD 2012;48:45-50
Change in platelet counts in 12 switch-over patients (with no off-ERT period): 12 months before and after switch
Plateau / asymptote after 2-5 years of treatment: normalization or irreversible changes or habituation?
CHANGES IN BIOMARKERS IN PATIENTS WITH TYPE 1 GAUCHER DISEASE TRANSITIONED FROM IMIGLUCERASE TO VELAGLUCERASE ALFA: CUMULATIVE 2-YEAR RESULTS FROM THE PHASE II/III TRIAL TKT034 AND EXTENSION

Ari Zimran, MD; Gregory M. Pastores, MD; Anna Tylki-Szymańska, MD; Derralynn A. Hughes, MD; Deborah Elstein, PhD; Rebecca Mardach, MD; Christine Eng, MD; Laurie Smith, MD; Margaret Heisel-Kurth, MD; Joel Charrow, MD; Paul Harmatz, MD; Paul Femhoff, MD; William Rhead, MD; Nicola Longo, MD; Pilar Giraldo, MD; David Zahrteh, MS; Eric Crombez, MD; Gregory A. Grabowski, MD

1Shaare Zedek Medical Center and Hebrew University-Hadassah Medical School, Jerusalem, Israel; 2New York University School of Medicine, New York, NY, USA; 3The Children’s Memorial Health Institute, Warsaw, Poland; 4University College London Medical School, London, UK; 5Kaiser Permanente, Los Angeles, CA, USA; 6Baylor College of Medicine, Houston, TX, USA; 7Children’s Mercy Hospitals and Clinics, Kansas City, MO, USA; 8Children’s Hospitals and Clinics of Minnesota, Minneapolis, MN, USA; 9Children’s Memorial Hospital, Chicago, IL, USA; 10Children’s Hospital & Research Center Oakland, Oakland, CA, USA; 11Emory University School of Medicine, Decatur, GA, USA; 12Children’s Hospital of Wisconsin, Milwaukee, WI, USA; 13University of Utah, Salt Lake City, UT, USA; 14Centro de Investigación Biomédica en Red de Enfermedades Parasitarias (CIBEREP) and Hospital Universitario Miguel Servet, Zaragoza, Spain; 15Shire Human Genetic Therapies, Inc., Lexington, MA, USA; 16Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, USA

FIGURE 2. Temporal changes from Baseline in plasma biomarkers
EFFECTS OF SWITCHING FROM REDUCED DOSE IMIGLUCERASE TO VELAGLUCERASE IN TYPE 1 GAUCHER DISEASE: CLINICAL AND BIOCHEMICAL OUTCOMES (SUBMITTED FOR PUBLICATION)

van Dussen L, Cox TM, Hendriks EJ, Morris E, Akkerman EM, Maas M, Groener JEM, Aerts JMFG, Deegan PB, Hollak CEM

- 32 adult GD1 patients from AMC and Adenbrooke’s Hospital
- switched to velaglucerase alfa after 1 - 8.5 months of imiglucerase dose reduction.
- parameters were studied at four time points: one year before the shortage, just before the shortage, before a switch to velaglucerase and after up to 1 year of treatment with velaglucerase.
- decreases in platelet counts as a result of reduced treatment with imiglucerase were quickly restored and chitotriosidase activity declined after switch.

Courtesy Profs. Carla Hollak & Tim Cox; accepted Haematologica 2012
Velaglucerase alfa: Summary

- Velaglucerase alfa may have an innate advantage because of wild type sequence and human cell system
- Lessons learned from Phase I/II are being corroborated by Phase III and EAP results
- Velaglucerase alfa appears to be less immunogenic
- **Switching from imiglucerase appears to be well-tolerated and may overcome a habituation effect**
- Response by hemoglobin, platelets, reduction in hepatosplenomegaly and improved bone mineral density as well as bone marrow burden score are robust and appear capable of approaching normal
- Therapeutic goals are achieved early and maintained
Thank you for giving me this challenging presentation