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Supplementary Materials for

Protein Replacement Therapies for Rare Diseases: A Breeze for Regulatory Approval?

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METHODS

Searching for MPRTs

Monogenic protein replacement therapies (MPRTs) were identified in a search of the following sources:

- U.S. orphan drug designation database (www.FDA.gov),
- European Union (EU) rare disease designations database (www.ema.europa.eu),
- Adis R&D Insight database [http://bi.adisinsight.com (subscription only)],
- Tufts CSDD (http://csdd.tufts.edu/research/databases),
- World Federation of Hemophilia (WFH) product listings (www.wfh.org)

and the pipelines of companies we know are active in the MPRT space:

- Sanofi (www.sanofi.com),
- Genzyme (www.genzyme.com),
- Shire (www.shire.com),
- Biomarin (www.bmrn.com),

- Bayer (www.bayer.com),
- Baxter (www.baxter.com),
- Commonwealth Serum Laboratories (CSL; www.csl.com.au),
- Bio Products Laboratory (www.bpl.co.uk),
- Sanquin (www.sanquin.nl/en),
- Octapharma (www.octapharma.com),
- Grifols (www.grifols.com),
- Talecris (www.talecrisplasma.com),
- LFB (www.lfb.fr/en),
- Pfizer (www.pfizer.com),
- Pharming (www.pharming.com),
- Novo Nordisk (www.novonordisk.com), and
- Zymogenetics (BMS) (www.bms.com).

For the orphan/rare disease designation databases, the full list of designated candidates and their respective indications were reviewed to identify MPRTs. For the Adis R&D Insight database, keyword searches were conducted on the terms "replacement therapy," "protein replacement," and "enzyme replacement." An Adis search was also conducted by using the database index phrase "blood coagulation factor." For the WFH product listing, all candidates identified as replacement factors marketed in the United States or EU were added to our MPRT list. Blood factors that were marketed for non-replacement therapy indications were excluded.

For the companies active in the MPRT space, we reviewed the candidates and indications on their pipeline pages to identify MPRTs. Because the focus of this research is approval probability once candidates enter trials, we did not attempt to identify discontinued preclinical programs.

Our approval probability analyses were restricted to MPRTs for the treatment of orphan diseases that had entered or completed clinical trials, filed for or received regulatory approval as of 30 November 2011.

Inclusion criteria

The study group excluded gene therapies, small molecules, hormones, and cofactors of enzymes. For inclusion, therapies had to meet the following criteria:

1. Approved or being evaluated in clinical trials as a protein replacement therapy for a rare disease, in which the protein replaces the product of a single defective gene. Diseases were confirmed to be the result of a single gene defect by identifying the gene and protein with Genetics Home Reference from the National Library of Medicine (http://ghr.nlm.nih.gov).
2. Approved or being evaluated in the United States or EU.
3. Native protein, novel formulation, or conjugate (such as pegylated protein or Fc fusion).

Candidate status was determined by means of review of the company pipeline for investigational products and by review of company or product websites for approved products. "Terminated" status was assigned to candidates in cases in which a company dropped a candidate from its pipeline or did not report any data for two or more years. Candidate status was recorded as the most advanced clinical phase or approval in either the United States or EU.

Comparing clinical trial timelines and trial size

We reviewed the approval packages (www.accessdata.fda.gov) for the MPRTs Elaprase, Vpriv, Fabrazyme, and Naglazyme to identify the number of patients evaluated in clinical trials and the drug approval month/year. To determine the Investigational New Drug (IND) application filing date, we searched Securities Exchange Commission (www.sec.gov) filings for Transkaryotic Therapies (TKT), Genzyme, and Biomarin. From the IND filing and approval dates, we calculated the development time for each candidate and compared them with the development timelines for new molecular entities and significant biologics (*9*, *10*). For the trial size comparison, we reviewed the Prescribing Information for approved biologic candidates for larger indications, including Remicade (www.remicade.com), Avastin (www.avastin.com), Stelara (www.stelara.com) and Herceptin (www.herceptin.com).

SUPPLEMENTARY TABLE

Table S1. Active MPRT preclinical candidates and MPRTs that have entered clinical development or received regulatory approval.

Candidate	Company	Status
Factor VIIa, Factor VII Deficiency		
Factor VII, Baxter	Baxter	Approved
Factor VII, BPL	Bio Products Laboratory	Approved
Factor VII, LFB	LFB	Approved
Novoseven/Novoseven RT	Novo Nordisk	Approved
Factor VIII, Hemophilia A		
Aafact	Sanquin	Approved
Advate	Baxter	Approved
Alphanate*	Grifols	Approved
Amofil	Sanquin	Approved
Beriate P	CSL Behring	Approved
Emoclot	Kedrion	Approved
Factane	LFB	Approved
Faktor VIII	Intersero	Approved
Fandhi	Grifols	Approved
Haemate P/Humate P*	CSL Behring	Approved
Haemoctin	Biotext	Approved
Hemofil	Baxter	Approved
Hyate-C	Ipsen	Approved
Immunate	Baxter	Approved
Koate-DVI	Talecris Biotherapeutics	Approved
Kogenate FS/Helixate FS/Helixate NexGen	Bayer/CSL Behring	Approved

Candidate	Company	Status
Monoclate-P	CSL Behring	Approved
Octanate	Octapharma	Approved
Octanativ	Octapharma	Approved
Optivate	Bio Products Laboratory	Approved
Recombinate	Baxter	Approved
Refacto	Pfizer/Wyeth	Approved
Replenate	Bio Products Laboratory	Approved
Xyntha/Refacto AF	Pfizer/Wyeth	Approved
8Y*	Bio Products Laboratory	Approved
Full-length recombinant FVIII, BAY81-8973	Bayer	Phase 3
LongAte, plasma-derived liposomal factor VIII, NecLip-pdFVIII	Recoly	Phase 3
Recombinant blood clotting Factor VIII, hcl-rFVIII	Octapharma	Phase 3
Recombinant factor VIII, NN7008, turoctocog alfa	Novo Nordisk	Phase 3
Recombinant human Coagulation Factor Viii Fc fusion protein	Biogen Idec	Phase 3
Recombinant porcine Factor Viii, B-domain deleted	Inspiration Biopharmaceuticals	Phase 3
NecLip-rFVIII, BAY 79-4980	Recoly/Bayer	Phase 2, terminated
Recombinant factor VIII, liposomal	Opperbas Holding/Omri Laboratories	Phase 2, terminated
Factor VIII, long-acting (glycopegylated), N8-GP, NN7088	Novo Nordisk	Phase 1
PEGylated B-domain deleted-rFVIII, BAY 94-9027	Bayer	Phase 1
Factor IX, Hemophila B		
Aimafix	Kedrion	Approved
Alphanine	Grifols	Approved

Candidate	Company	Status
Berinin-P	CSL Behring	Approved
Benefix	Pfizer/Wyeth	Approved
Betafact	LFB	Approved
Factor IX Grifols	Grifols	Approved
Faktor IX	Biotest	Approved
Immunine	Baxter	Approved
Mononine	CSL Behring	Approved
Nanotiv	Octapharma	Approved
Nonafact	Sanquin	Approved
Octanine F	Octapharma	Approved
Replenine-VF	Bio Products Laboratory	Approved
Recombinant Factor IX, BAX 326	Baxter Healthcare Corp	Phase 3
Recombinant Factor IX, IB1001	Inspiration Biopharmaceuticals	Phase 3
Recombinant human coagulation Factor IX, fusion protein	Biogen Idec	Phase 3
rFIX, glyco-PEGylated derivative, N9-GP, NN7999	Novo Nordisk	Phase 3
Factor IX (rIX-FP) albumin fusion protein, CSL 654	CSL Behring	Phase 1/2
Factor IX	Novo Nordisk/Zymogenetics	Phase 1, terminated
Factor IX - CTP	Prolor Biotech	Preclinical
Factor X, Factor X deficiency		
Factor X P Behring	CSL Behring	Approved
Human Factor X	Bio Products Laboratory	Phase 3
Factor XI, Factor XI deficiency		
Factor XI, BPL	Bio Products Laboratory	Approved
Hemoleven	LFB	Approved
Factor XIII, Factor XIII deficiency		

Candidate	Company	Status
Corifact/Fibrogammin P	CSL Behring	Approved
Factor Xiii [A2} homodimer, Recombinant Dna Origin, NN1841	Novo Nordisk	Phase 3
vWF/vWF + FVIII, von Willebrand disease		
Alphanate*	Grifols	Approved
Haemate P/Humate P*	CSL Behring	Approved
Wilate	Octapharma	Approved
Willfact	LFB	Approved
8Y*	BPL	Approved
Recombinant von Willebrand Factor (Rhvwf), BAX111	Baxter	Phase 3
Protein C, Protein C deficiency		
Ceprotin	Baxter	Approved
Protexel	LFB	Approved
Antithrombin III, Antithrombin deficiency		
Aclotine	LFB	Approved
Anbinex	Grifols	Approved
ATIII	Bio Products Laboratory	Approved
Atnativ	Pharmacia	Approved
Atryn	GTC Biotherapeutics	Approved
Thrombate III	Grifols	Approved
Kybernin P	CSL Behring	Approved
Antithrombin III recombinant, KW-3357	Kyowa Hakko Kirin	Phase 1
Fibrinogen, Fibrinogen deficiency		
Clottagen	LFB	Approved
Riastap/Haemocomplettan P	CSL Behring	Approved
Recombinant human fibrinogen	Pharming	Preclinical

Candidate	Company	Status
C1-esterase inhibitor, Hereditary angioedema		
Berinert	CSL Behring	Approved
C1-inhibitor (human) vapor heated, immuno	Baxter	Approved
Cetor	Sanquin	Approved
Cinryze	ViroPharma	Approved
Ruconest	Pharming	Approved
C1 esterase inhibitor (human)	iBio	Preclinical
Alpha-1 proteinase inhibitor, alpha1-Proteinase Inhibitor Deficiency		
Aralast/Aralast NP	Baxter	Approved
Glassia	Kamada/Baxter	Approved
Prolastin/Prolastin-C	Talecris	Approved
Zemaira	CSL Behring	Approved
Transgenic human α-1 antitrypsin	PPL/Bayer	Phase 2, terminated
Recombinant human α-1 antitrypsin (Raat)	Arriva Pharmaceuticals	Phase 1/2, terminated
Alpha-1 antitrypsin	iBio	Preclinical
Glucocerebrosidase, Gaucher Disease		
Ceredase	Genzyme	Approved
Cerezyme	Genzyme	Approved
Vpriv	Shire	Approved
Uplyso	Protalix Biotherapeutics	Phase 3
Lysodase, PEG-glucocerebrosidase	NIH/Enzon	Phase 1, terminated
α-L-Iduronidase, Mucopolysaccharidosis I		
Aldurazyme	BioMarin	Approved
Idua-Hirmab fusion protein, Agt-181	ArmaGen Technologies	Preclinical
Iduronate sulfatase, Mucopolysaccharidosis II		

Candidate	Company	Status
Elaprase	Shire	Approved
IgG-enzyme fusion protein, Agt-182	ArmaGen Technologies	Preclinical
***N*-acetylgalactosamine-4-sulfatase/Arylsulfatase B, Mucopolysaccharidosis VI**		
Naglazyme	BioMarin	Approved
***N*-acetylgalactosamine-6-sulfatase, Mucopolysaccharidosis IVA**		
BMN-110, recombinant *N*-acetylgalactosamine-6-sulfatase	BioMarin	Phase 3
Lysosomal enzyme *N*-acetylgalactosamine-6-sulfate sulfatase	Vivendy Therapeutics	Preclinical
Heparan sulfate sulfatase, Mucopolysaccharidosis IIIA		
HGT 1410, heparan sulfate sulfatase	Shire	Phase 1/2
α-Galactosidase A, Fabry disease		
Fabrazyme	Genzyme	Approved
Replagal	Shire	Approved
α-Galactosidase A	Pharming	Phase 2, terminated
α-Galactosidase A, plant-produced	iBio	Preclinical
α-Glucosidase, Pompe disease		
Lumizyme	Genzyme	Approved
Myozyme	Genzyme	Approved
BMN-701, Recombinant glycosylated independent lysosomal targeting (GILT) tagged human acid α-glucosidase	BioMarin	Phase 1
α-Glucosidase, transgenic	Genzyme/Pharming	Phase 2, terminated
Pompase, α-glucosidase, recombinant, mammalian cell	Synpac	Phase 1, terminated
Recombinant human highly phosphorylated acid α-glucosidase, neo-GAA	Genzyme	Preclinical
Protein replacement, Pompe	Oxyrane	Preclinical

Candidate	Company	Status
Acid sphingomyelinase, Niemann-Pick type B disease		
Acid sphingomyelinase, recombinant, rhASM	Genzyme	Phase 1
α-Mannosidase, α-Mannosidosis		
Lamazym	Zymenex	Phase 2
Arylsulphatase A, Metachromatic leukodystrophy		
Metazym	Shire	Phase 2, terminated
Arylsulfatase A (Rharsa), HGT-1110	Shire	Preclinical
Lysosomal acid lipase, LAL Deficiency		
SBC-102, recombinant human LAL	Synageva BioPharma	Phase 1/2
Sucrase-isomaltase, Sucraseisomaltase deficiency		
Sucraid	QOL Medical	Approved
Adenosine deaminase, Adenosine deaminase deficiency		
Adagen	Sigma-Tau Pharmaceuticals	Approved
IGF-1, Primary IGF-1 deficiency		
Increlex	Ipsen	Approved
Somatomedin-1, mecasermin	Biogen Idec/Pharmacia	Approved
Alkaline phosphatase, Hypophosphatasia		
ENB-0040, human recombinant fusion protein, alkaline phosphatase	Enobia Pharma	Phase 2
Porphobilinogen deaminase, Acute intermittent porphyria		
Recombinant human porphobilinogen deaminase	Zymenex	Phase 2, terminated
Galactocerebrosidase, Krabbe Disease		
Recombinant human galactocerebrosidase	ACE Biosciences	Preclinical
Plasminogen, Plasminogen deficiency		
Human plasminogen	Kedrion	Preclinical

Candidate	Company	Status
Alpha-*N*-acetyl glucosaminidase, Mucopolysaccharidosis IIIB		
rhNAGLU, SBC-103	Synageva	Preclinical
HGT 3010	Shire	Preclinical
Factor H, Factor H deficiency		
Complement Factor H	LFB	Preclinical
Type VII collagen, Dystrophic epidermolysis bullosa		
Recombinant human type VII collagen	Lotus Tissue Repair	Preclinical
Ectodysplasin - A1, X-linked hypohidrotic ectodermal dysplasia		
Fusion protein consisting of human IgG1 constant region Fc region fused to the human receptor binding domain of ectodysplasin-A1	Edimer Pharmaceuticals	Preclinical
Thymidine phosphorylase, Mitochondrial neurogastrointestinal encephalopathy disease		
Recombinant thymidine phosphorylase encapsulated with autologous erythrocytes	St. George's University of London	Preclinical
Palmitoyl protein thioesterase-1, Palmitoyl protein thioesterase-1 deficiency		
Human recombinant palmitoyl protein thioesterase-1 (PPT1)	University of Texas Southwestern Medical Center	Preclinical
Frataxin, Friedreich's Ataxia		
TAT-Frataxin (TAT-FXN)	Indiana University School of Medicine, Wake Forest University School of Medicine	Preclinical
NPC2 protein, Niemann-Pick type C2 disease		
NPC2	University, Aarhus, Denmark, Dublin Institute of Technology, Wadsworth Center	Preclinical
Lecithin-cholesterol acyltransferase (LCAT)		
Recombinant human LCAT	AlphaCore Pharma	Preclinical

*Approved for both Hemophilia A and von Willebrand Disease.