



# Spark Therapeutics, Inc.

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Corporate Overview  
February 2018

## Forward-looking statements

This presentation contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including statements regarding the company's product candidates, including LUXTURNA™ (voretigene neparovec-rzyl), *SPK-7001*, *SPK-9001* and *SPK-8011*. The words "anticipate," "believe," "expect," "intend," "may," "plan," "predict," "will," "would," "could," "should," "continue" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in, or implied by, such forward-looking statements. These risks and uncertainties include, but are not limited to, the risk that: (i) our MAA for LUXTURNA may not be approved by EMA; (ii) the data from our Phase 3 clinical trial of LUXTURNA may not support labeling for all biallelic *RPE65* mutations other than Leber congenital amaurosis (LCA) in ex-US geographies; (iii) the improvements in functional vision demonstrated by LUXTURNA in our clinical trials may not be sustained over extended periods of time; (iv) voretigene neparovec may not be approved in any markets outside of the U.S.; (v) upon approval, Novartis may not be successful in commercializing or selling voretigene neparovec in one or more markets; (vi) we may not receive any additional milestone or royalty payments from Novartis; (vii) our early preliminary clinical results for our product candidate, *SPK-8011*, for hemophilia A may not be sustained or sufficient to support further development; (viii) we may be unsuccessful in achieving higher factor VIII activity levels through dose escalation in our Phase 1/2 clinical trial of *SPK-8011*; (ix) our early preliminary data in our Phase 1/2 clinical trial of *SPK-8011* have yet to be audited and therefore are subject to confirmation in connection with a clinical trial audit; (x) we do not enter into agreements with Harvard Pilgrim, Express Scripts subsidiaries or other commercial insurers to make LUXTURNA available for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy; (xi) payers, health benefit providers, physicians and hospitals do not believe access to therapy is a shared responsibility; (xii) our payer and patient offerings will not ensure eligible patients have the coverage and financial support they need to gain access to LUXTURNA and the required specialized medical care; (xiii) payers terminate any agreements they enter into with us; (xiv) our proposal to the Centers for Medicare & Medicaid Services (CMS) is not accepted; (xv) our lead *SPK-FIX* product candidate, *SPK-9001*, may not produce sufficient data in our Phase 1/2 clinical trial to warrant further development; (xvi) interim data from our *SPK-7001* Phase 1/2 clinical trial, including data to be generated from our recently expanded cohort, may not support further development of this product candidate; and (xvii) any one or more of our product candidates in preclinical or clinical development will not successfully be developed and commercialized. For a discussion of other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the "Risk Factors" section, as well as discussions of potential risks, uncertainties and other important factors, in our Annual Report on Form 10-K, our Quarterly Reports on Form 10-Q and other filings we make with the Securities and Exchange Commission. All information in this press release is as of the date of the release, and Spark undertakes no duty to update this information unless required by law.



LUXTURNA™ is the trademark of Spark Therapeutics, Inc.

# Spark is a fully integrated gene therapy platform company seeking to challenge the inevitability of genetic disease

- **LUXTURNA approved by FDA, the first ever gene therapy** for a genetic disease in the US
  - US launch underway
  - EU registration **in process**, with **ex-US rights** licensed to **Novartis Pharmaceuticals**
- Investigational **SPK-9001** for **hemophilia B** Phase 1/2 compelling safety and clinical outcomes data published in *New England Journal of Medicine*
  - Moving towards **finalizing transition to Pfizer**
- Investigational **SPK-8011** for **hemophilia A** initial Phase 1/2 data provide **proof-of-concept**
  - **7 participants infused as of 12/4/17** at three doses:  $5 \times 10^{11}$  vg/kg;  $1 \times 10^{12}$  vg/kg; and  $2 \times 10^{12}$  vg/kg
  - **Dose-finding underway** with data in 2Q/3Q18
- A **fully-integrated** adeno-associated virus (**AAV**) **gene therapy platform and pipeline** of clinical and preclinical candidates across multiple target tissues:
  - **First and only FDA-approved AAV commercial manufacturing facility**
  - **Follow-up ongoing** for investigational **SPK-7001** Phase 1/2 trial **in choroideremia**
  - **New** liver-directed disease **target: Pompe disease** program in development utilizing technology from **Genethon**
- Approximately **\$540 million** in cash and equivalents at 12/31/17 plus **\$105 million received from Novartis Pharmaceuticals** in 1Q18; **Priority Review Voucher**



# Introducing LUXTURNA (voretigene neparvovec-rzyl)

# LUXTURNA is the first FDA-approved gene therapy for a genetic disease

## FDA-approved labeling for LUXTURNA

- Provides **genetic indication** without regard to phenotypic diagnosis
- **No** FDA-imposed **upper age limit**
- Eligibility of *RPE65* patients is left to the **clinical judgment of the treating physician**
- Labeling supports claim of **durability out to three years**
- Clearly described **safety profile**



LUXTURNA in EU registration process with action expected in 3Q18

Ex-US rights licensed to Novartis Pharmaceuticals\*



\*Terms include \$105MM upfront, an additional \$25MM on EMA approval, up to an aggregate \$40MM on initial sales in certain ex-US markets and a flat mid-twenties percent royalty on net sales.

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Investor communication only: Not for use in promotion

# LUXTURNA U.S. launch drivers and enablers



Find additional eligible patients

Drive *RPE65* genetic testing



Enable conversion of known patients

Educate on clinical value



Operationalize ocular gene therapy treatment centers

Leverage robust patient support programs



Secure coverage through traditional and novel models

Seamless supply chain

# Spark offering three novel payment and distribution options to support patient access to LUXTURNA



## Options for novel payment and distribution models

### Innovative Contracting Model (ICM)

**Direct sale** to payer or specialty pharmacy as an alternative to traditional “buy and bill” model

- **Reduces financial burden and risk** to the institution as well as mark-up to the payer
- **Coverage to label; expedited benefits** processing; patient **out-of-pocket cap**

### Outcomes-based rebate arrangement

**Outcomes-based rebate** arrangement with both:

- A short-term **efficacy** (30-90 days) **measure**
- A longer-term **durability** (30 months) **measure**

### On-going discussions with Centers for Medicare & Medicaid Services (CMS)

Proposal to enable Spark to directly offer government and commercial payers the option to make **payments in installments**, while **providing flexibility** for greater **outcomes-based rebates**

**LUXTURNA wholesale acquisition cost: \$425,000 per eye**



Demonstrated leadership in applying gene therapy technology to hemophilia



# Spark objectives for developing an optimized gene therapy for hemophilia

- **Safety**

- **Low**, effective **dose** to reduce risk of SAEs
- **Restore hemostasis by leveraging innate biology** rather than bypassing normal physiological pathways
- **No new risks or inhibitors**

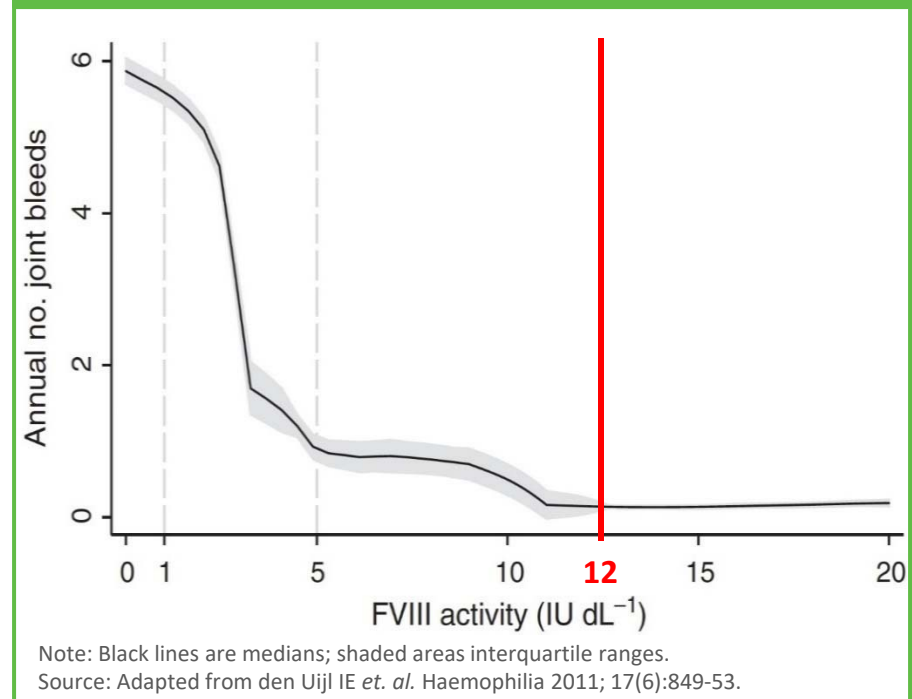
- **Predictable clinical outcomes**

- Participants **achieving clinically meaningful outcomes based on sufficient factor activity** without exceeding Factor levels that could introduce new safety risks




- **Sustained** factor expression

- Without the troughs that characterize regular infusions of protein therapeutics
- Reduce treatment burden and improve QoL

**Factor activity levels >12% at all times reduces risk of bleeds and need for chronic infusions**



# Spark is two for two in achieving proof-of-concept in hemophilia gene therapy

	<b>SPK-9001</b> for hemophilia B  	<b>SPK-8011</b> for hemophilia A 
<b>Safety</b>	<ul style="list-style-type: none"> <li><b>No SAEs reported</b>, including no FIX inhibitors and no thrombotic events as of November 29, 2017</li> </ul>	<ul style="list-style-type: none"> <li><b>No SAEs reported</b>, including no FVIII inhibitors and no thrombotic events as of December 6, 2017</li> </ul>
<b>Evidence of predictability of clinical outcomes</b>	<ul style="list-style-type: none"> <li><b>Predictability of clinical outcomes: 97% reduction in mean ABR<sup>1</sup> and 99% reduction in mean AIR<sup>1</sup></b> in more than 13 cumulative years of follow-up, as of November 29</li> <li><b>Consistent FIX activity</b> levels achieved                             <ul style="list-style-type: none"> <li>All <b>11 participants</b> well within an <b>acceptable range</b></li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li><b>First 4 participants free of bleeds</b> beginning 4-weeks post-vector infusion, with <b>98% reduction in mean AIR<sup>1</sup></b> in ~2 cumulative years of follow-up as of December 6, 2017</li> <li>As of 12/6/17, <b>three additional participants</b> have been dosed (1 at <math>1 \times 10^{12}</math> and 2 at <math>2 \times 10^{12}</math>)</li> <li><b>Therapeutic FVIII levels</b> seen in <b>first 4 participants</b>: average factor levels after 12 weeks for <math>5 \times 10^{11}</math> participants of 10% and 16% and for <math>1 \times 10^{12}</math> participants of 9% and 13% as of December 6, 2017</li> </ul>
<b>Evidence of sustainability</b>	<ul style="list-style-type: none"> <li><b>Sustained FIX expression</b> with 4 participants with FIX reads out over 18 months post-infusion and 5 others out over one year as of November 29, 2017</li> </ul>	<ul style="list-style-type: none"> <li>First participant out over 9 months, and second, third and fourth participants out ~3-6 months post-infusion as of December 6, 2017</li> </ul>

Data as of November 29<sup>th</sup>, 2017 (latest update) for *SPK-9001* and December 6<sup>th</sup>, 2017 for *SPK-8011*.

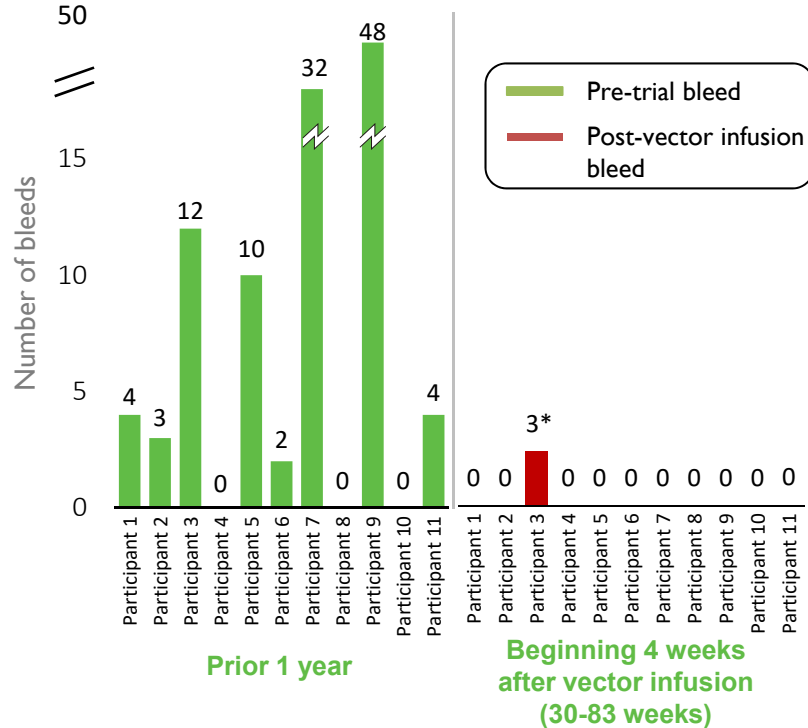
**Note:** Two *SPK-9001* trial participants experienced asymptomatic, transient elevation in liver enzymes, or decline in FIX activity, potentially indicative of an immune response to the Spark100 capsid. Both received a tapering course of corticosteroids (now completed) after which their ALTs returned to baseline, while factor IX activity levels have remained stable. As of Nov. 29, neither participant had experienced a bleed nor taken factor concentrates. Participants 3 and 4 in *SPK-8011* Phase 1/2 trial were put on tapering course of corticosteroids after drop in FVIII activity levels observed; prednisone stopped on November 28th and 26th, respectively.

**Source:** *SPK-8011* and *SPK-9001* preliminary initial Phase 1/2 data per trial database. Factor activity refers to FVIII:C or FIX:C values from local labs.

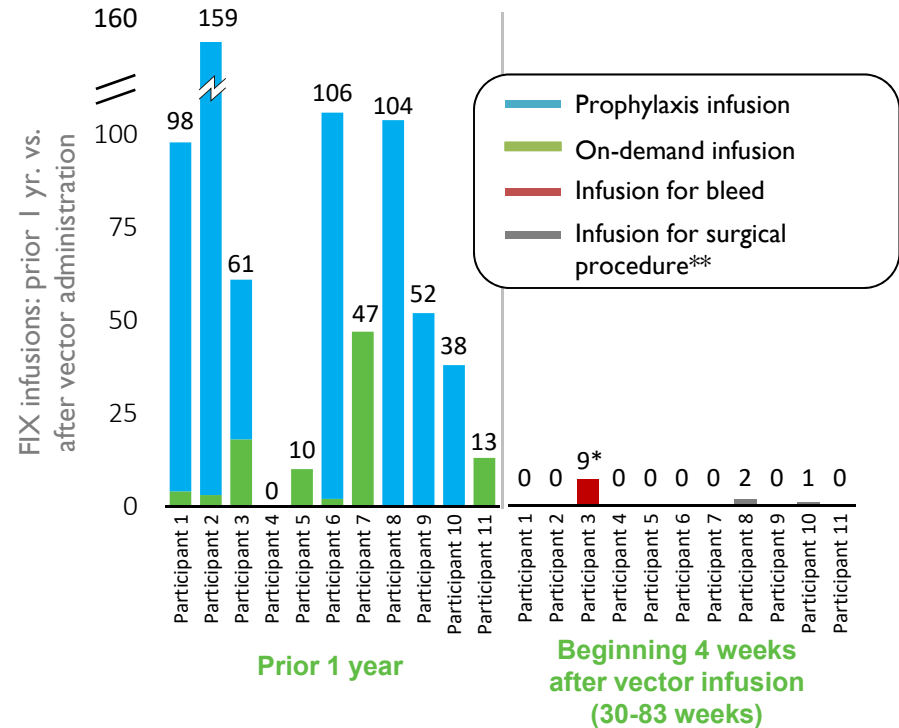
1) Calculated beginning 4 weeks post-vector infusion.

# Preliminary SPK-9001 Phase 1/2 data in hemophilia B: Predictable clinical outcomes for all 11 participants as demonstrated by near elimination of bleeds and infusions

**97% reduction in mean ABR beginning 4 weeks after vector infusion (95% beginning at time of vector infusion)**



**99% reduction in mean AIR beginning 4 weeks after vector infusion (97% beginning at time of vector infusion)**

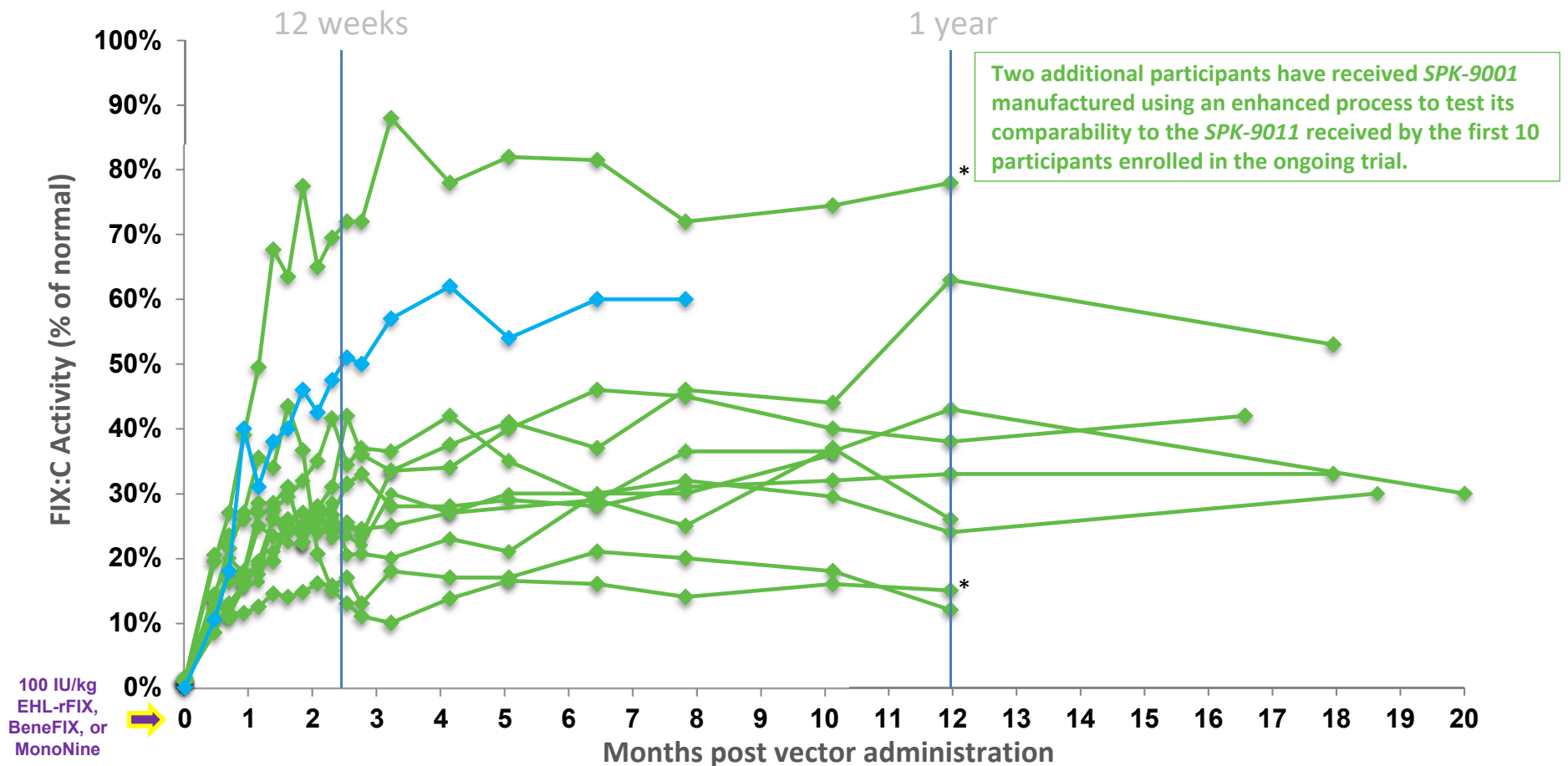


Note: SPK-9001 data as of last visit prior to November 29, 2017; most recent update.

\*Participant 3 self-infused factor concentrates for ankle bleed on Day 2 after vector infusion and self-administered precautionary infusions another nine times between Dec. 1, 2016 and Jan 2, 2017 for persistent knee pain. Participant has not used factor concentrates since Jan. 2.

\*\* Participant 8 received infusions for removal of mediport; Participant 10 received infusion for surgical procedure.

# Preliminary SPK-9001 Phase 1/2 data in hemophilia B: Consistent and sustained FIX activity within target range in initial 11 participants



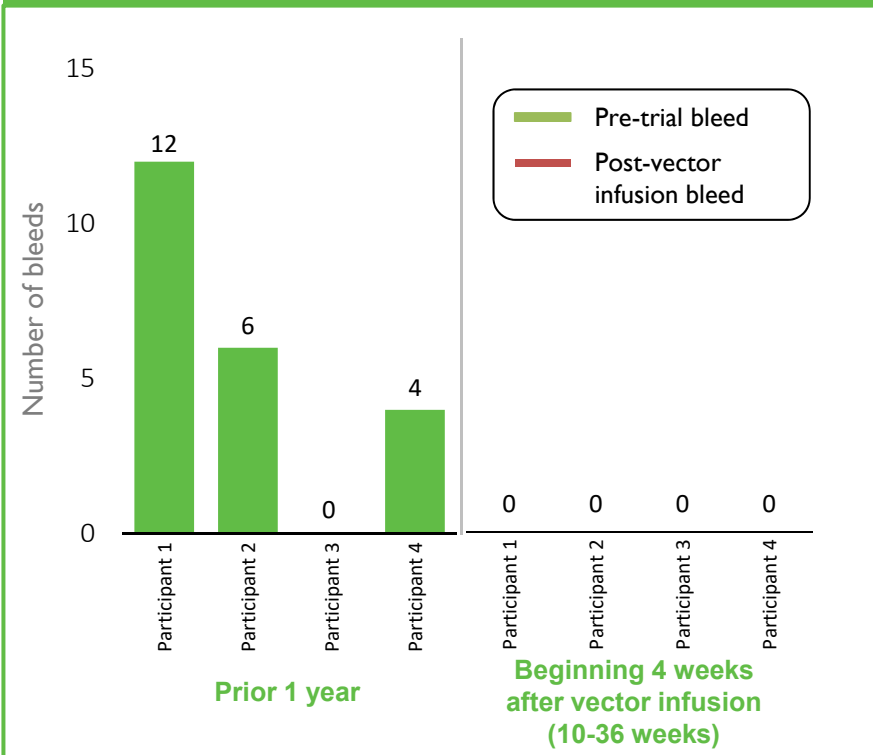
Note: Plotted values represent average of reads for each patient each week for the first 12 weeks, and +/- 2 weeks for each point thereafter.  
 Source: Spark data as of Nov. 29, 2017;  
 FIX:C Activity = circulating factor IX activity level  
 EHL-rFIX – Extended half-life recombinant factor IX

\*These two participants experienced asymptomatic, transient elevation in liver enzymes, or decline in FIX activity, potentially indicative of an immune response to the Spark100 capsid. Both received a tapering course of corticosteroids (now completed) after which their ALTs returned to baseline, while factor IX activity levels remained stable. As of November 29<sup>th</sup>, neither participant had experienced a bleed nor taken factor concentrates.

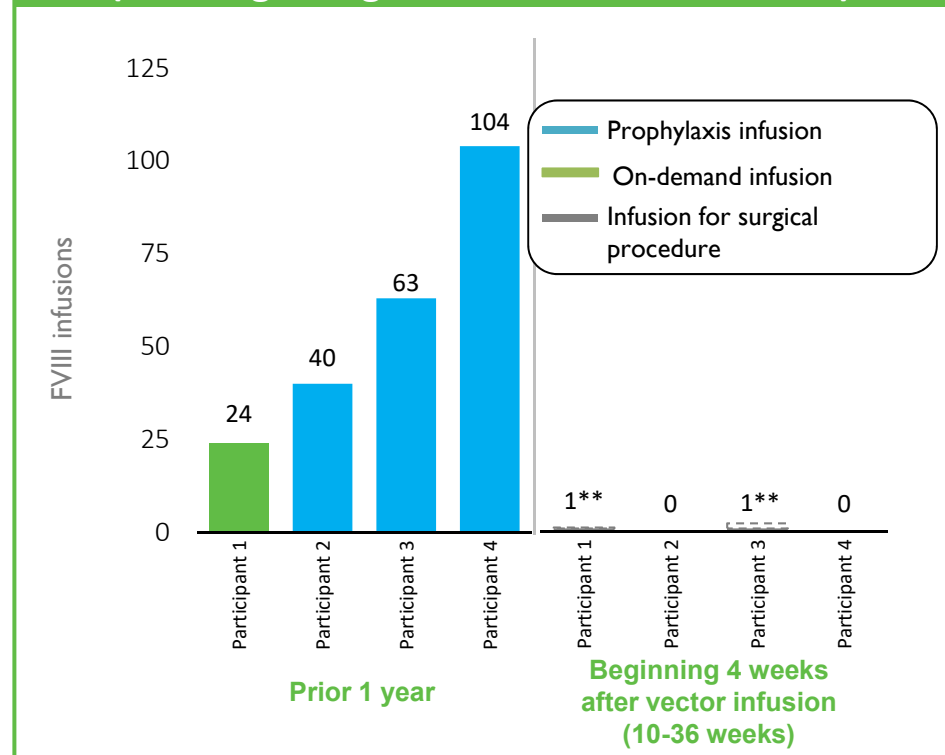


# Preliminary SPK-8011 Phase 1/2 data in hemophilia A: Clinical outcomes for first 4 participants demonstrated by near elimination of bleeds and infusions

100% reduction in mean ABR in first 4 participants beginning 4 weeks post-vector infusion (82% beginning at time of vector infusion)



98% reduction in mean AIR in first 4 participants beginning 4 weeks post-vector infusion (96% beginning at time of vector infusion)








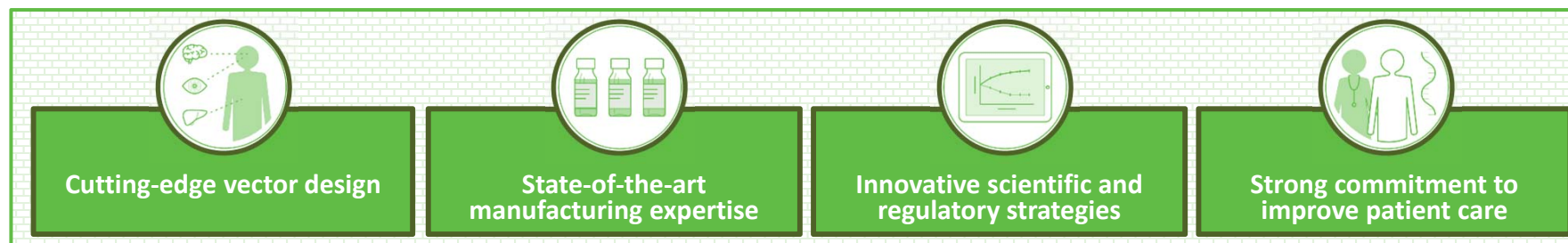
Note: SPK-8011 data as of December 6, 2017; Dotted boxes denote AIR extrapolated from infusions.  
 \*\*Participants 1 and 3 both received an infusion of factor for dental extraction procedures.



# Fully-integrated AAV gene therapy platform and pipeline

# Spark development pipeline

Preclinical	Phase 1/2	Phase 3	Registration
 <b>INHERITED RETINAL DISEASES (IRDs)</b>			
LUXTURNA (voretigene neparvovec): IRD due to biallelic <i>RPE65</i> mutations (EU)*			
SPK-7001: Choroideremia			
LHON <sup>1</sup>			
Undisclosed			
 <b>LIVER-DIRECTED DISEASES</b>			
SPK-9001: Hemophilia B			
SPK-8011: Hemophilia A			
SPK-GAA: Pompe disease <sup>2</sup>			
 <b>NEURODEGENERATIVE DISEASES</b>			
CLN2 disease <sup>3</sup>			
Huntington's disease			

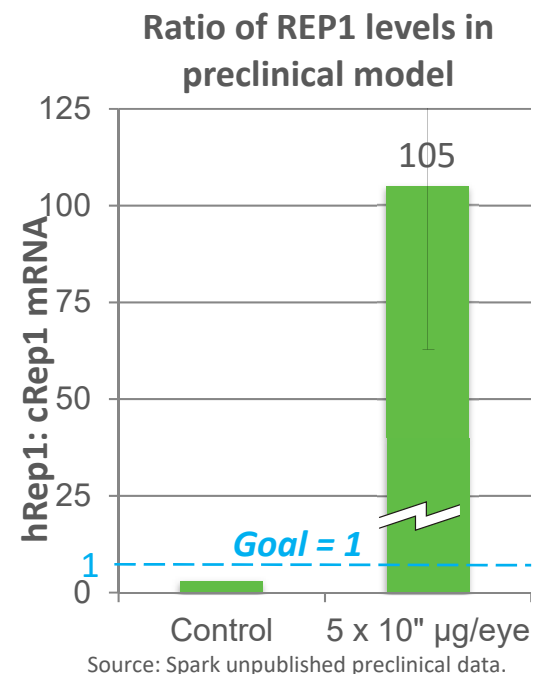


<sup>1</sup>Leber hereditary optic neuropathy; <sup>2</sup>Initial construct licensed from Genethon; <sup>3</sup>Form of Batten Disease.

\*Approved in the US; MAA validated and under review in EU, with ex-US rights licensed to Novartis.

# Interim data from ongoing *SPK-7001* Phase 1/2 trial in CHM: No product-related SAEs with 15 participants dosed; follow-up ongoing

- Choroideremia is slow-progressing, affecting ~**12,500** males in US / EU5
- To study safety, initiated 2-year Phase 1/2 trial in 10 participants with later-stage disease
  - *SPK-7001* administration resulted in **no product-related SAEs**
  - At interim analysis<sup>1</sup>, 4 of 10 later-stage participants showing **non-statistically significant indications of efficacy** on 1 or more endpoints
- Non-significance of results may be due to duration of follow-up and later-stage of disease in this cohort
- **Completed enrollment in** additional cohort of 5 participants at an **earlier-stage of disease**
- **Next steps:** Additional analyses of earlier- and later-stage disease cohorts to be conducted in 2018





# Investigational *SPK-GAA* for Pompe disease: Optimized to address drawbacks of standard of care (SoC) by leveraging Spark's liver-directed gene therapy expertise to deliver a proprietary engineered transgene

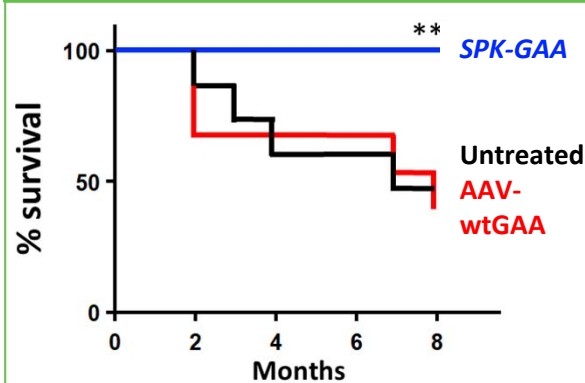
## Shortcomings of current SoC: GAA enzyme replacement

- Replacement of recombinant form of missing enzyme (*wtGAA*) results in limited efficacy in many affected patients
- Lengthy (3-5 hours every 2 weeks) and costly infusions
- Potential for immunogenicity in some patients

## *SPK-GAA* points of differentiation

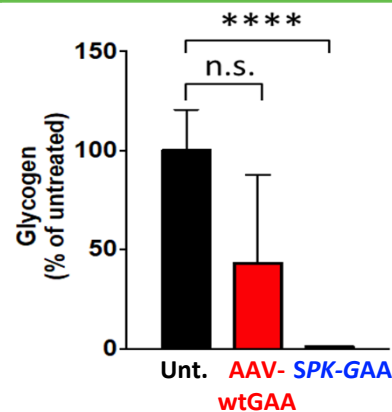
- Novel *GAA* transgene (licensed from Genethon) engineered for superior secretion and therapeutic effect
- Potential for greater glycogen clearance than ERT with AAV-mediated continuous elevation in *GAA* levels
- Evidence of reduced immunogenicity of secreted (vs. native) *GAA* in Pompe mice

***SPK-GAA*'s secretable *GAA* transgene expression results in superior rescue of Pompe mouse model vs. AAV-*wtGAA***



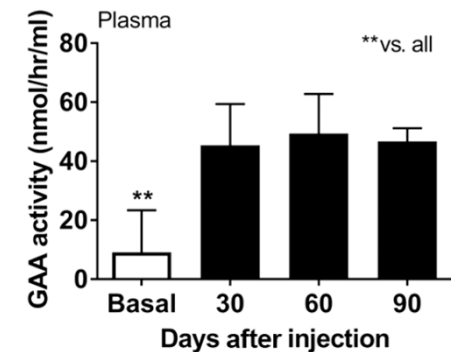
Source: Puzzo et al., Science Translational Medicine 2017 and unpublished results

***SPK-GAA* gene transfer in Pompe mouse model results in superior clearance of glycogen from muscle**



Source: Puzzo et al., Science Translational Medicine 2017

***GAA* activity levels observed in NHP plasma at *SPK-GAA* dose of  $2 \times 10^{12}$  vg/kg (levels therapeutic in mouse model)**



Source: Puzzo et al., Science Translational Medicine 2017 and unpublished results

Next steps: IND-enabling work in 2018

Estimated prevalence / incidence: ~6,000-8,000 / ~200-400 in US + EU5



\*\*p<0.01, \*\*\*\*p<0.0001

# Spark's AAV manufacturing facility is the first and only FDA-approved commercial AAV manufacturing facility in the US

## Manufacturing processes in use

- Purpose-built, multi-suite, **in-house cGMP facility**
- Adherent-cell culture (HEK293 mammalian cell line), transient transfection process
- Implemented a scalable all-column downstream purification process
- Technology capable of being scaled linearly
- **50+ sub-lots** manufactured to date at Spark
- **24 assays** developed for, and being used in, production of LUXTURNA





Sufficient scale for IRDs (including LUXTURNA™) and Hemophilia B

## Processes currently being implemented

- Spark has achieved **proof-of-concept** in a fully scalable, serum-free **suspension cell culture system** utilizing our current HEK293 cell line
- **Ongoing scale-up and implementation** of new upstream and downstream processes
  - Leveraging **Brammer Bio** facilities and capabilities to execute on **Spark-developed process**
- **Scale-up** currently **tracking in-line** with plans to have suspension process support Hem A clinical supply needs

Designed to support anticipated requirements for Hemophilia A and other future potential products

# Looking forward to 2018

Preclinical	Phase 1/2	Phase 3	Registration
 <b>INHERITED RETINAL DISEASES (IRDs)</b>			
LUXTURNA (voretigene neparvovec): IRD due to biallelic <i>RPE65</i> mutations (EU)*			
SPK-7001: Choroideremia			
 <b>LIVER-DIRECTED DISEASES</b>			
SPK-9001: Hemophilia B			
SPK-8011: Hemophilia A			
SPK-GAA: Pompe disease <sup>1</sup>			

## IRD catalysts

- ✓ **January 2018:** Investigational LUXTURNA ex-US rights licensed to Novartis
- **End of 1Q18:** LUXTURNA available in the United States
- **3Q18:** LUXTURNA regulatory action by EMA
- **2018:** Update on maturing SPK-7001 dataset

## Liver-directed disease catalysts

- **1Q18:** Complete enrollment of additional SPK-9001 Phase 1/2 participants
- **2Q/3Q18:** SPK-8011 Phase 1/2 clinical data update
- **2018:** Complete IND-enabling studies for SPK-GAA for Pompe