# Spark Therapeutics, Inc.

36th Annual J.P. Morgan Healthcare Conference

January 8, 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 neparvovec-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) our early preliminary clinical results for our product candidate, *SPK-8011*, for hemophilia A may not be sustained or sufficient to support further development; (v) we may be unsuccessful in achieving higher factor VIII activity levels through dose escalation in our Phase 1/2 clinical trial of *SPK-8011*; (vi) 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; (vii) 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; (viii) payers, health benefit providers, physicians and hospitals do not believe access to therapy is a shared responsibility; (ix) 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; (x) payers terminate any agreements they enter into with us; (xi) our proposal to the Centers for Medicare & Medicaid Services (CMS) is not accepted; (xii) our lead *SPK-FIX* product candidate, *SPK-9001*, may not produce sufficient data in our Phase 1/2 clinical trial to warrant further development; (xiii) 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 (xiv) 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.

# 2017 was a trailblazing year

- **LUXTURNA approved by FDA,** the **first ever gene therapy** for a genetic disease in the US
  - **US launch underway** with **EU** registration **in process**
- Investigational ***SPK-9001*** for **hemophilia B** Phase 1/2 compelling safety and clinical outcomes data published in *New England Journal of Medicine*
  - Moving toward **transition to Pfizer**
- Investigational ***SPK-8011*** for **hemophilia A** initial Phase 1/2 data provide **proof-of-concept**:
  - **7 participants infused to date** at three doses: $5x10^{11}$ vg/kg; $1x10^{12}$ vg/kg; and $2x10^{12}$ vg/kg
  - **Dose-finding** work **in process** supported by accelerated enrollment
- 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**
- **$539 million** in cash, cash equivalents and marketable securities at December 31, 2017 and received a **Priority Review Voucher** in connection with LUXTURNA's approval

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# Introducing LUXTURNA (voretigene neparvovec-rzyl)

# LUXTURNA approved in US; MAA validated and under review in EU

**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™
voretigene neparvovec-rzyl
for subretinal injection

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

**LUXTURNA in EU registration process with action expected in 3Q18**

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# LUXTURNA U.S. launch drivers and enablers





| | | | |
|---|---|---|---|
| **Find additional eligible patients** | **Enable conversion of known patients** | **Operationalize ocular gene therapy treatment centers** | **Secure coverage through traditional and novel models** |
| **Drive *RPE65* genetic testing** | **Educate on clinical value** | **Leverage robust patient support programs** | **Seamless supply chain** |

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# 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<br>• **Reduces financial burden and risk** to the institution as well as mark-up to the payer<br>• **Coverage to label; expedited benefits** processing; patient **out-of-pocket cap** |
| **Outcomes-based rebate arrangement** | **Outcomes-based rebate** arrangement with both:<br>• A short-term **efficacy** (30-90 days) **measure**<br>• 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**

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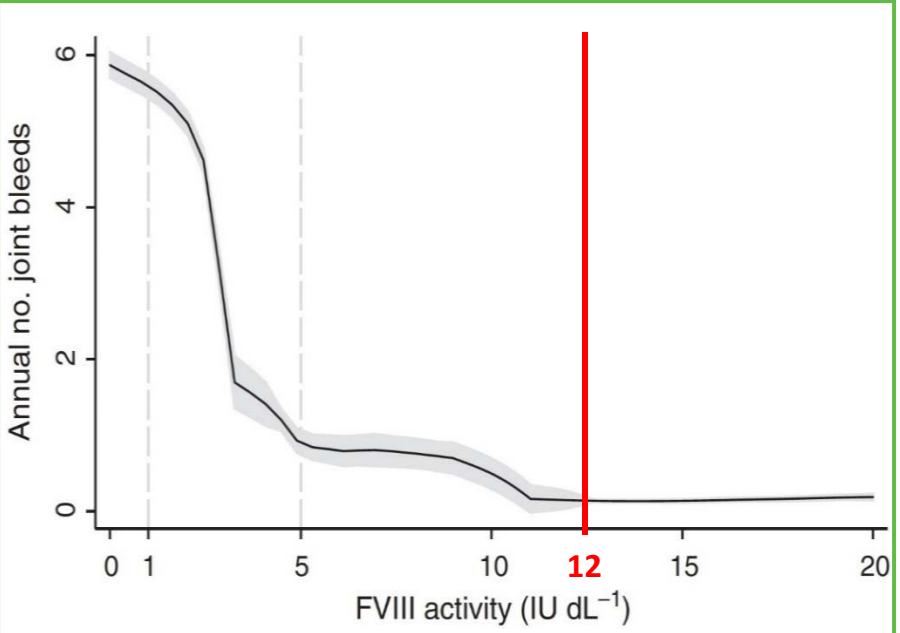
# Demonstrated leadership in applying gene therapy technology to hemophilia

# 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**




Note: Black lines are medians; shaded areas interquartile ranges.
Source: Adapted from den Uijl IE *et. al.* Haemophilia 2011; 17(6):849-53.

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

| | *SPK-9001* for hemophilia B (Spark, Pfizer) | *SPK-8011* for hemophilia A (Spark) |
|---|---|---|
| **Safety** | • **No SAEs reported**, including no FIX inhibitors and no thrombotic events as of November 29, 2017 | • **No SAEs reported**, including no FVIII inhibitors and no thrombotic events as of December 6, 2017 |
| **Evidence of predictability of clinical outcomes** | • **Predictability of clinical outcomes: 97% reduction in mean ABR[1] and 99% reduction in mean AIR[1]** in more than 13 cumulative years of follow-up, as of November 29<br>• **Consistent FIX activity** levels achieved<br>– All **11 participants** well within an **acceptable range** | • **First 4 participants free of bleeds** beginning 4-weeks post-vector infusion, with **98% reduction in mean AIR[1]** in ~2 cumulative years of follow-up as of December 6, 2017<br>• As of 12/6/17, **three additional participants** have been dosed (1 at $1x10^{12}$ and 2 at $2x10^{12}$)<br>• **Therapeutic FVIII levels** seen in **first 4 participants**: average factor levels after 12 weeks for $5x10^{11}$ participants of 10% and 16% and for $1x10^{12}$ participants of 9% and 13% as of December 6, 2017 |
| **Evidence of sustainability** | • **Sustained FIX expression** with 4 participants with FIX reads out over 18 months post-infusion and 5 others out over one year as of November 29, 2017 | • First participant out over 9 months, and second, third and fourth participants out ~3-6 months post-infusion as of December 6, 2017 |

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

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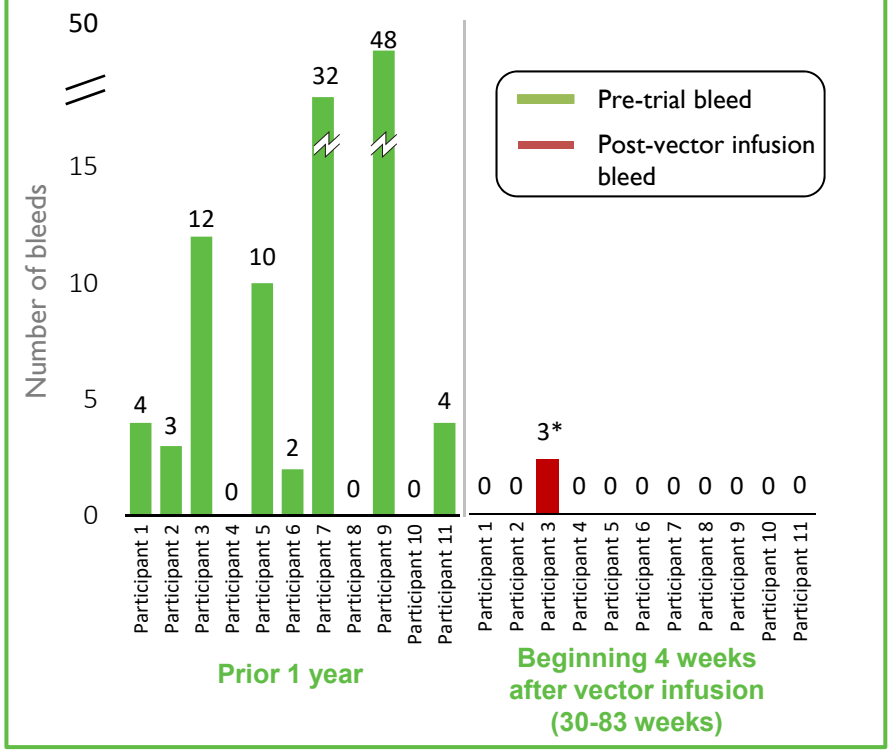
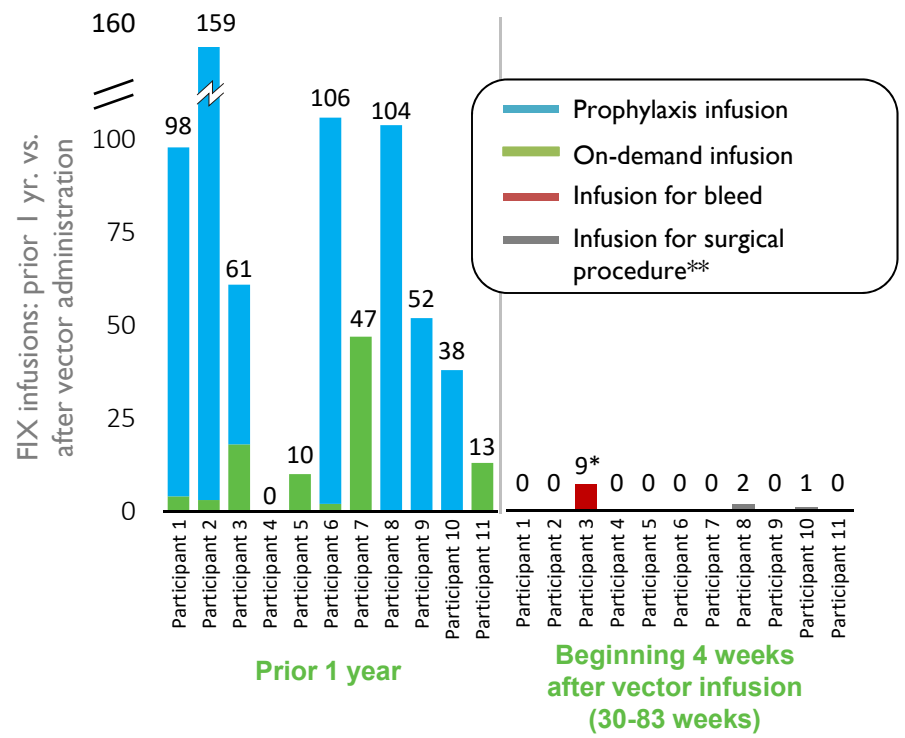
# Preliminary *SPK-9001* Phase 1/2 data in hemophilia B: Predictable clinical outcomes for all 11 participants as demonstrated by near elimination of bleeds and infusions

**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)**

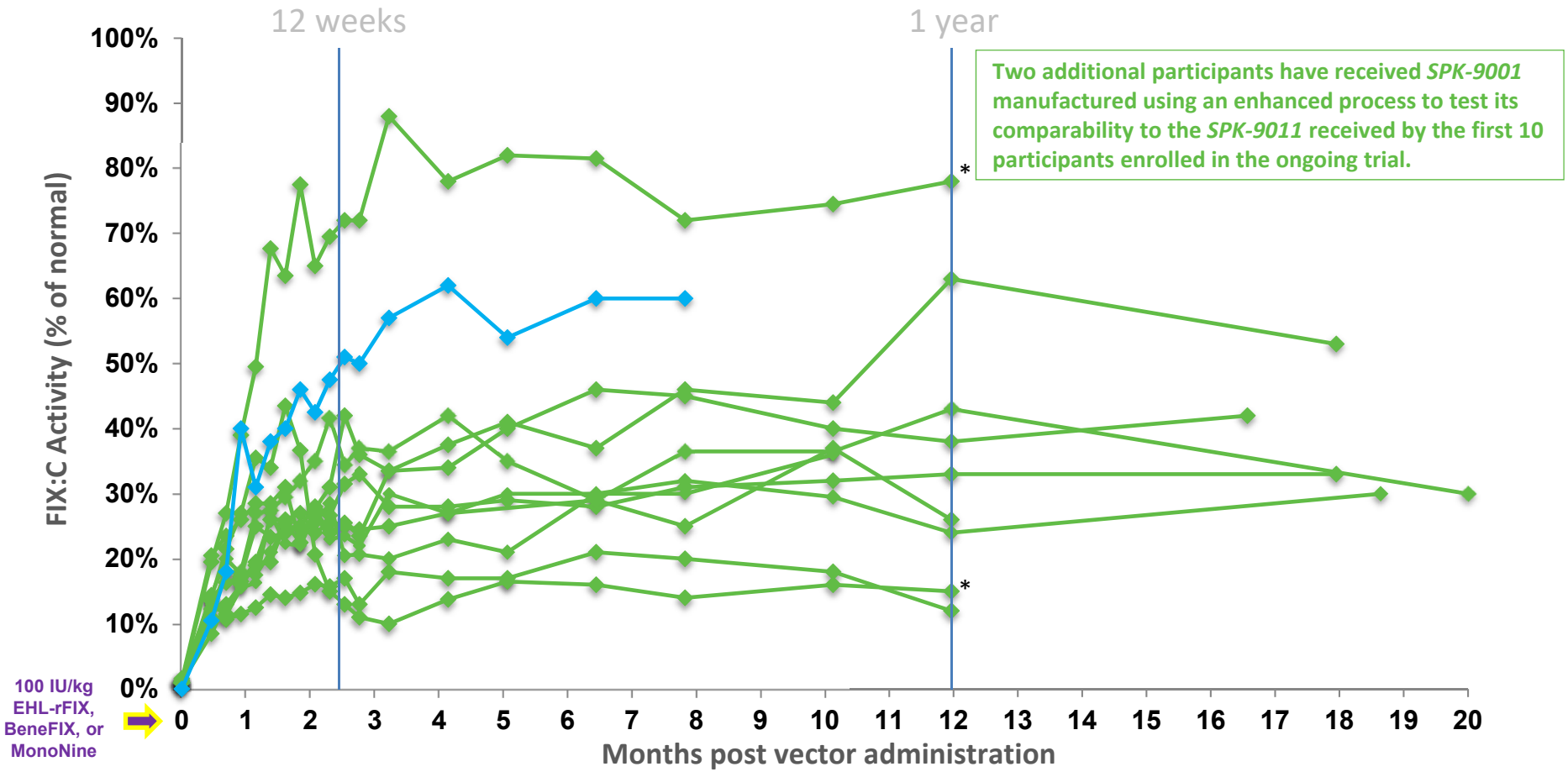



**Note: *SPK-9001* data as of last visit prior to November 29, 2017; most recent update.**

*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



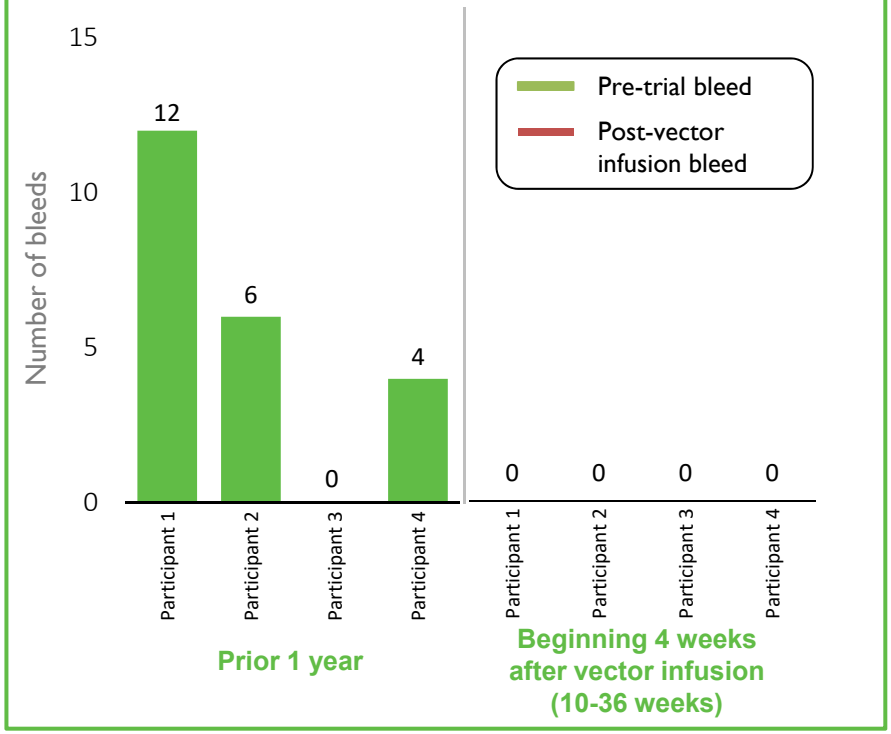

**Two additional participants have received *SPK-9001* manufactured using an enhanced process to test its comparability to the *SPK-9011* received by the first 10 participants enrolled in the ongoing trial.**

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

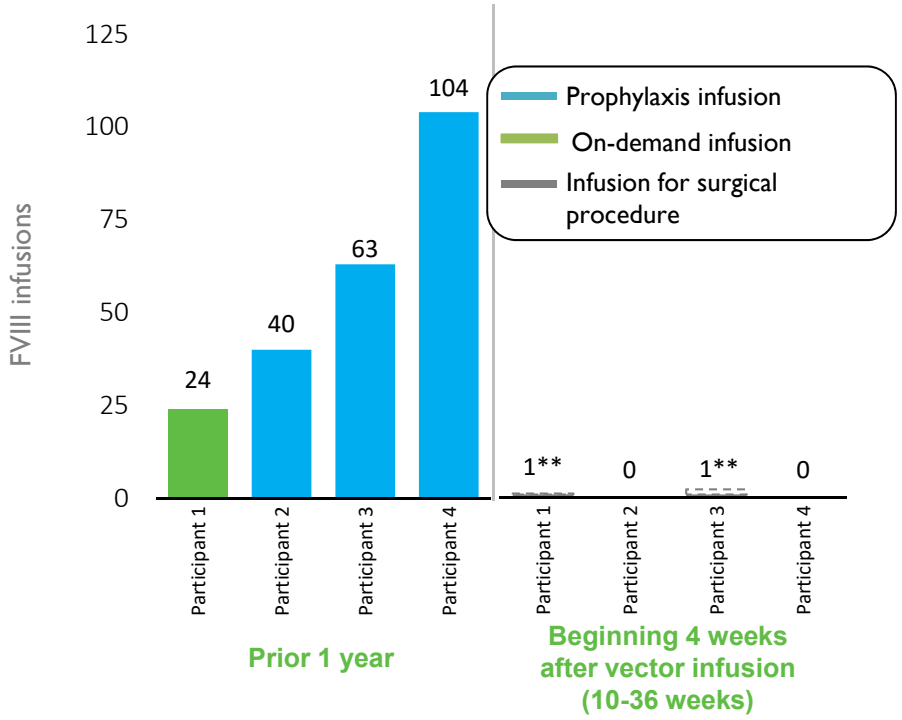
*These two participants experienced asymptomatic, transient elevation in liver enzymes, or decline in FIX activity, potentially indicative of an immune response to the Spark100 capsid. Both received a tapering course of corticosteroids (now completed) after which their ALTs returned to baseline, while factor IX activity levels remained stable. As of November 29th, 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)**

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**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.

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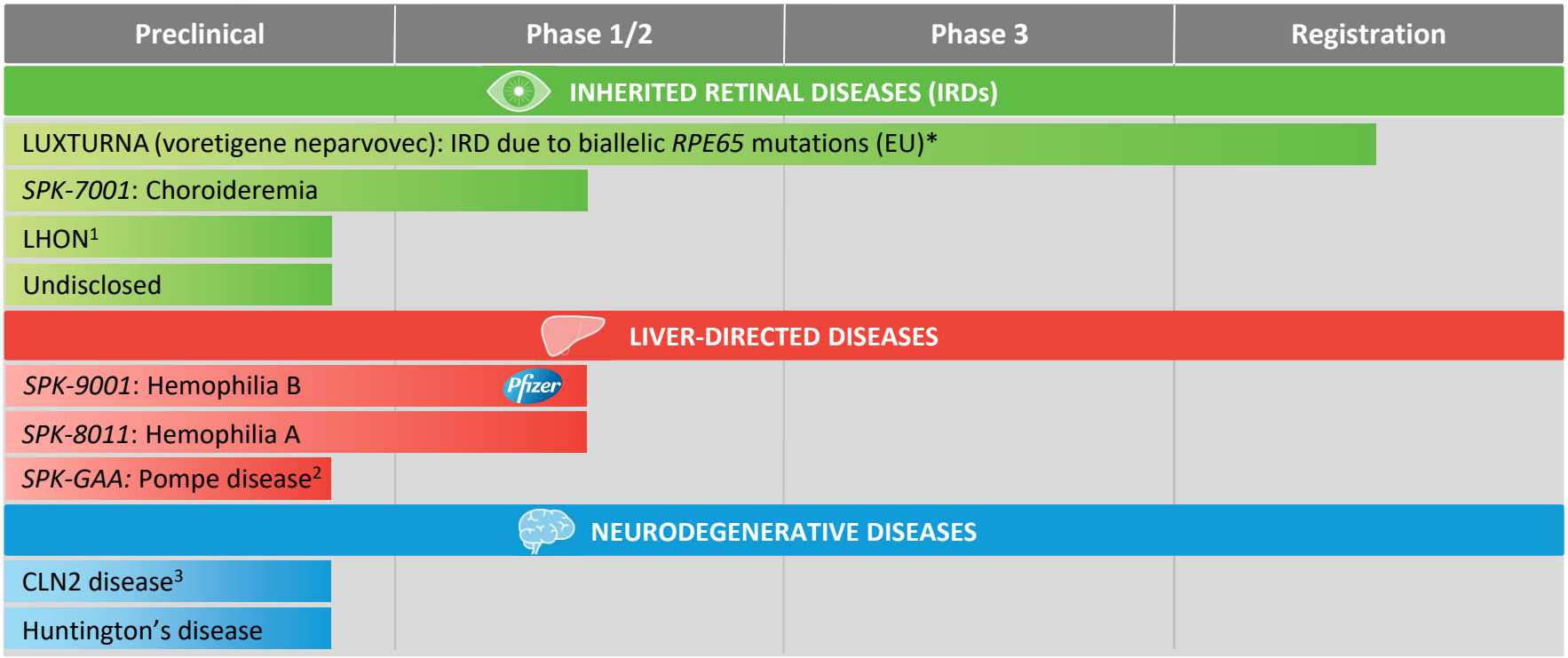
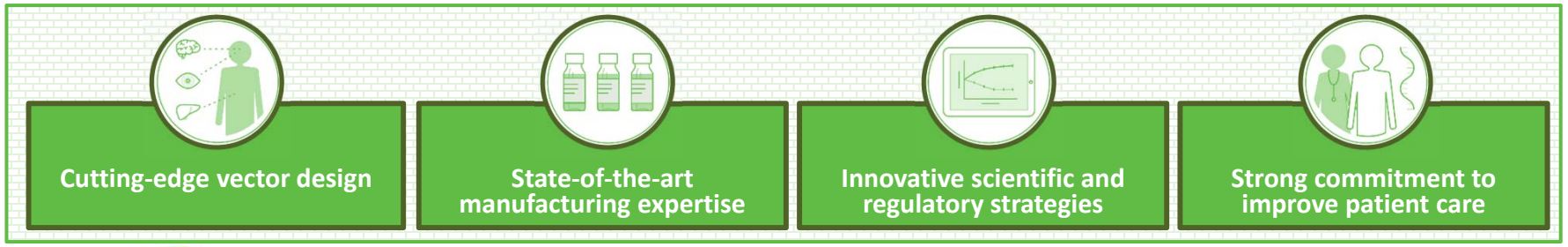
# Fully-integrated AAV gene therapy platform and pipeline

# Spark development pipeline

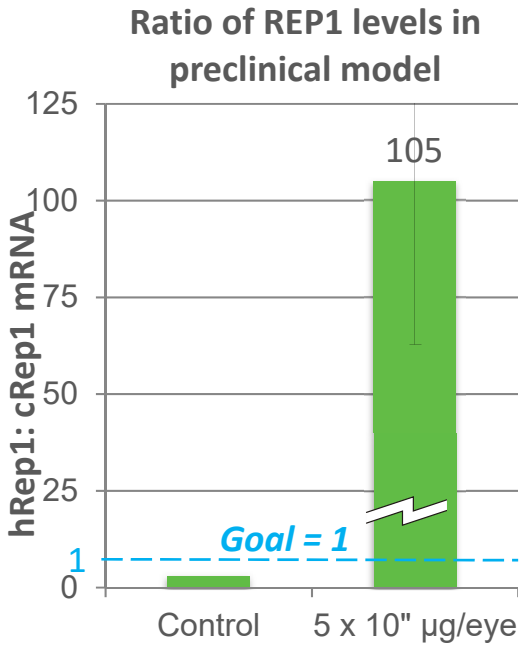



[1]Leber hereditary optic neuropathy; [2]Initial construct licensed from Genethon; [3]Form of Batten Disease.
*Approved in the US; MAA validated and under review in EU.

# 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[1], 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



Source: Spark unpublished preclinical data.

[1] At time of interim analysis (May 2017), had 1 year of follow-up on 5 participants, 18 months of follow-up on 4 and the targeted 2-year data for 1

# 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

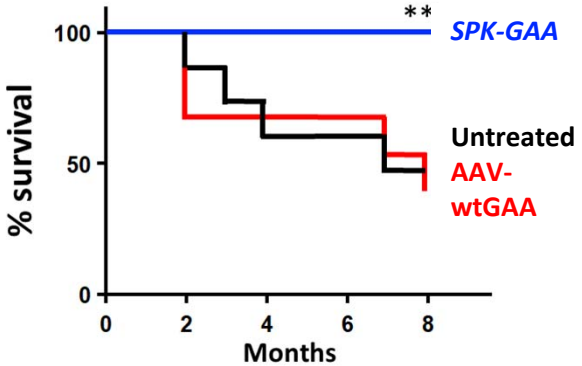
***Shortcomings of current SoC: GAA enzyme replacement***

- 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***

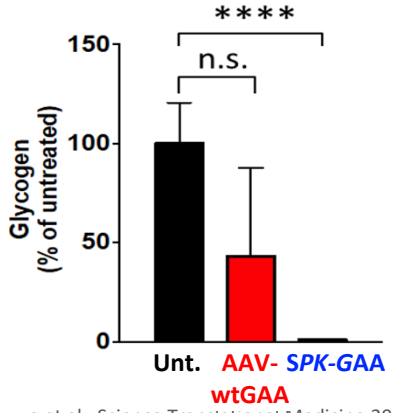
- Novel *GAA* transgene (licensed from Genethon) engineered for superior secretion and therapeutic effect
- Potential for greater glycogen clearance than ERT with AAV-mediated continuous elevation in *GAA* levels
- Evidence of reduced immunogenicity of secreted (vs. native) *GAA* in Pompe mice

**_SPK-GAA's_ secretable _GAA_ transgene expression results in superior rescue of Pompe mouse model vs. AAV-wtGAA**



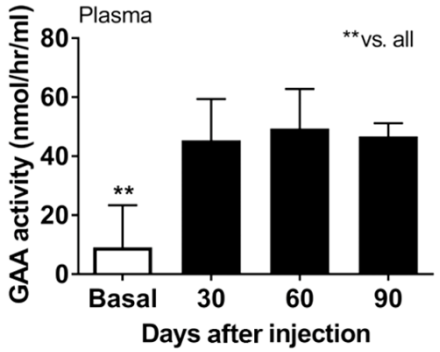

Source: Puzzo et al., Science Translational Medicine 2017 and unpublished results

**_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 $2x10^{12}$ 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

## 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

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

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

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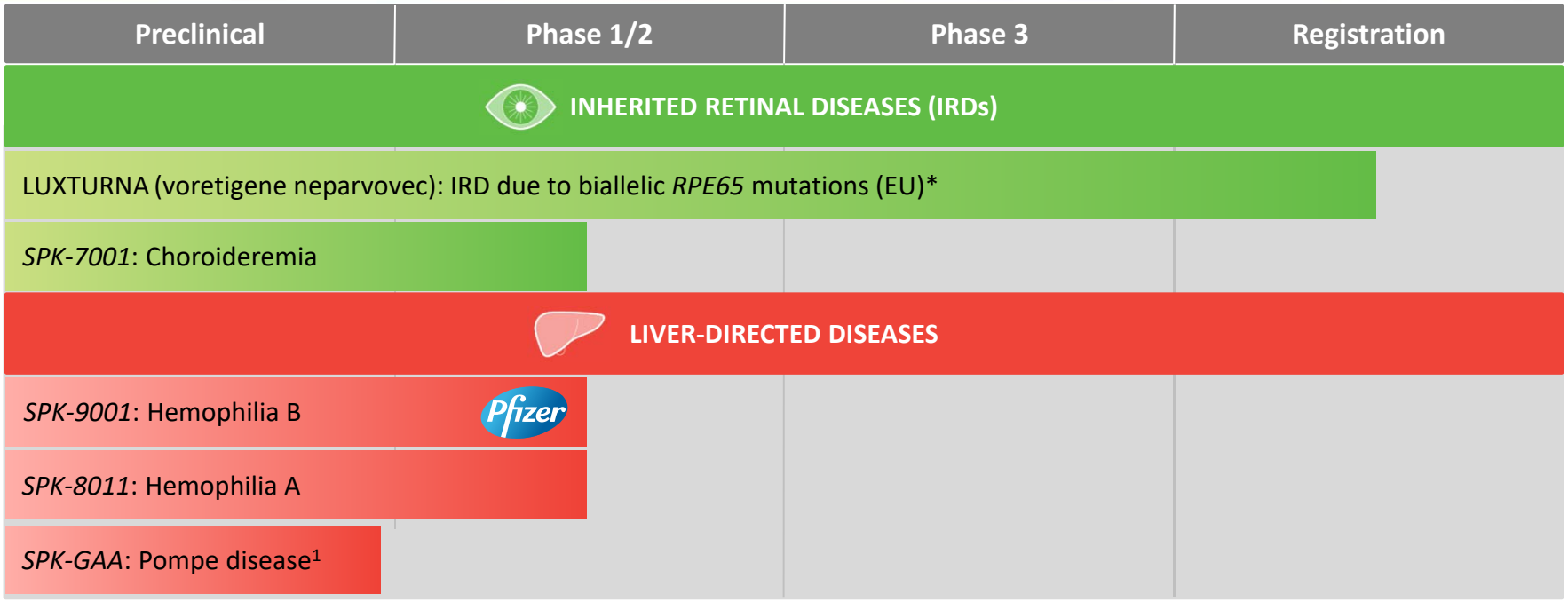
# Looking forward to 2018




**IRD catalysts**

- **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

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*Approved in the US; MAA validated and under review in EU.
[1]Initial construct licensed from Genethon.