Payor Guidance Follow Up: Execution and Real World Challenges

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Advertising and Promotion for Medical Products Conference

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Michael S. Labson

October 17, 2019

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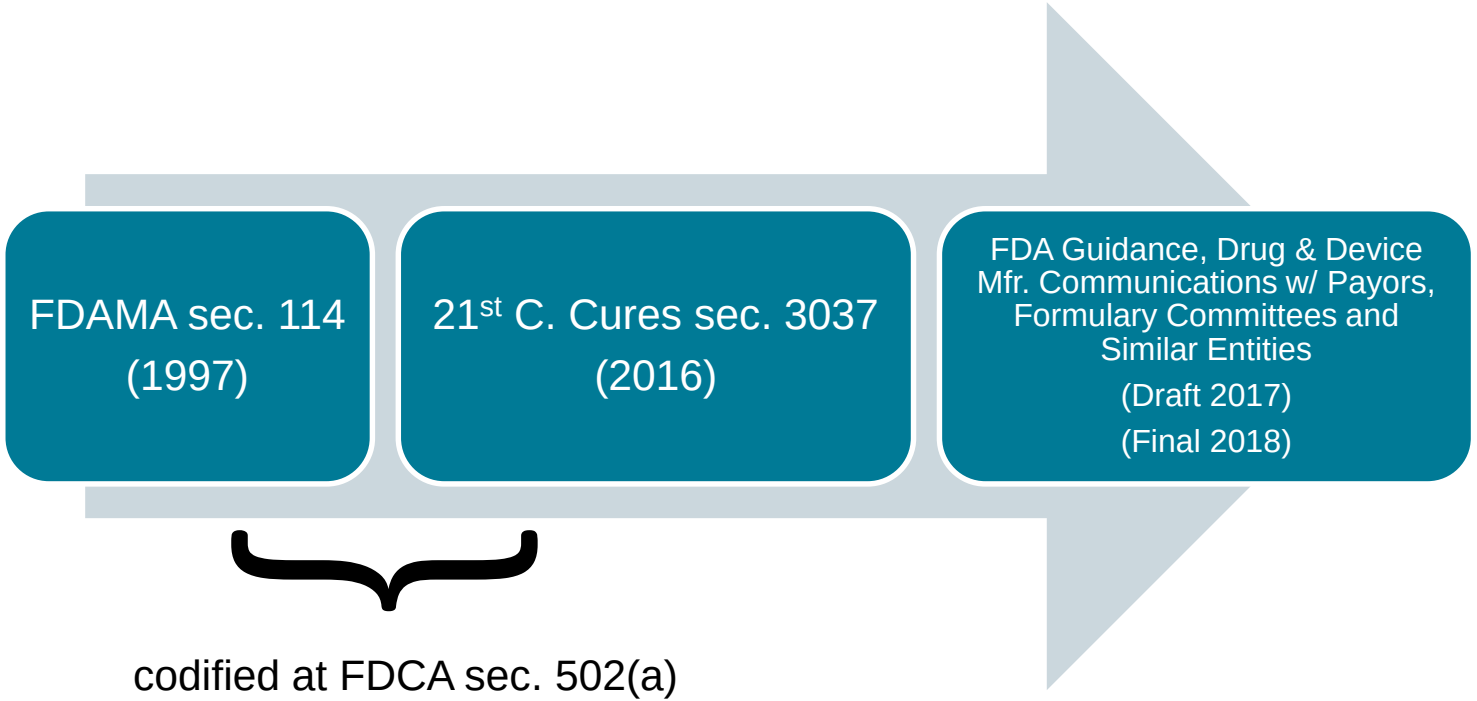
Background

Evolving Rules for Communications to Payors



Healthcare Economic Information to Payors on Approved Products

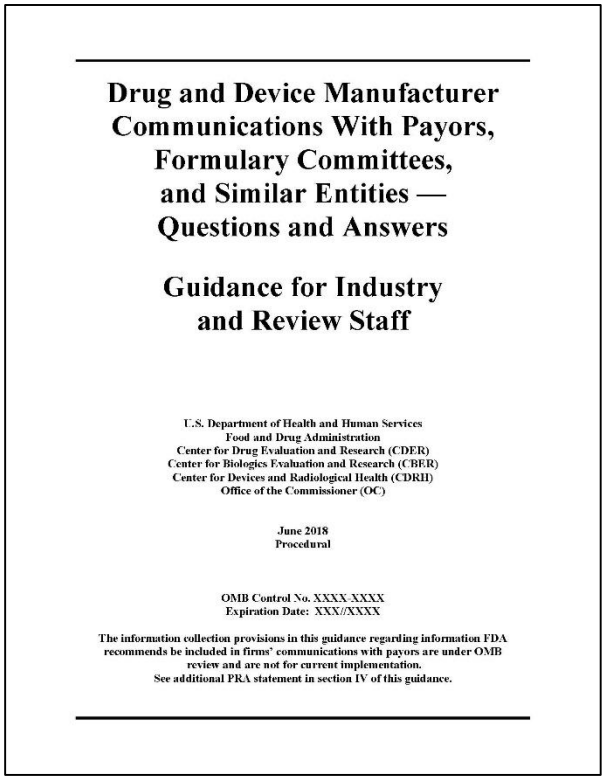
Healthcare economic information (HCEI) …

... to payors, formulary committees, and similar entities …

… related to an approved indication …

supported by competent and reliable scientific evidence (CARSE)

Unapproved Products and Uses



Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities — Questions and Answers

Guidance for Industry and Review Staff

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of the Commissioner (OC)

June 2018
Procedural

OMB Control No. XXXX-XXXX
Expiration Date: XXX//XXXX

The information collection provisions in this guidance regarding information FDA recommends be included in firms' communications with payors are under OMB review and are not for current implementation.
See additional PRA statement in section IV of this guidance.

- Product information (e.g., drug class)
- Indication sought, including endpoints and populations studied
- "Factual presentations of results from studies, including clinical studies … (i.e., no characterizations or conclusions should be made regarding the safety or effectiveness of the unapproved product or unapproved use)"
- Anticipated timeline for FDA action
- Product pricing information
- Patient utilization projections
- Product-related programs/services (e.g., patient support programs)

Question & Challenges in Practice

(Some) Questions & Challenges in Practice

1) Scope of eligible audience
   a) What entities are “similar” to payors and formulary committees?
   b) Are advisors to P&T decision-makers eligible?
   c) How to document eligibility?
2) Scope of pre-approval communications
   a) Who from a company may communicate pre-approval information?
   b) May HCEI be communicated pre-approval?
3) What is an HCEI analysis?
4) What is CARSE (and how does it relate to substantial evidence, SASS, truthful/non-misleading)?
5) How to treat communications around value-based contracts?
6) What are standards for communicating HCEI to other (non-payors) audiences?

Thank You!

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Disclaimer

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The Payor Guidance in Action: The Experience of Spark Therapeutics

Paul Savidge
US General Counsel
Spark Therapeutics
October 17, 2019

DISCLAIMER

The views and opinions expressed are not intended as legal advice on any particular issue.

They reflect an interpretation of FDA guidance as applied to a specific experience.

Presentation is for educational purposes only and is not intended to promote the use of any product.

COMMUNICATIONS TO PAYORS REGARDING INVESTIGATIONAL DRUGS AND DEVICES

"Payors have indicated that due, in part, to their need to, in some situations, plan for and make coverage and reimbursement decisions far in advance of the effective date of such decisions, they are ...interested in receiving information ...about medicinal products that are not yet approved by FDA for any use and about unapproved uses of approved medicinal products."

OUR DILEMMA

Gene therapy represents an entirely new approach to health care

If approved, voretigene neparvovec would be the very first gene therapy for a genetic disease in the United States

- *Would treat a disease for which there was no medical treatment*

Very low levels of understanding among payors of gene therapy or how it would work

Very low levels of understanding among payors of the clinical development program supporting voretigene neparvovec

Very low levels of understanding among payors of how they might value the benefit of this investigational product for purposes of reimbursement

Because of the progressive nature of the genetic disease (a form of blindness), it was critical that the therapy be available to appropriate patients through payors as quickly as possible post-approval.

COMMUNICATIONS TO PAYORS REGARDING INVESTIGATIONAL DRUGS AND DEVICES

21 CFR 312.7(a) limited how firms could communicate information regarding investigational new drugs, including to payors

(a) *Promotion of an investigational new drug.* A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

Pre-guidance, firms would primarily rely on the unprompted/unsolicited questions from payors about investigational therapies

COMMUNICATIONS TO PAYORS REGARDING INVESTIGATIONAL DRUGS AND DEVICES

"When the following types of information about unapproved products or unapproved uses provided by firms to payors are unbiased, factual, accurate and non-misleading…FDA does not intend to object … [to] such communications as evidence of a new intended use [and] does not intend to enforce any applicable postmarketing submission requirements for these materials."

COMMUNICATIONS TO PAYORS REGARDING INVESTIGATIONAL DRUGS AND DEVICES

Types of information firms may communicate to payors about investigational products or uses:

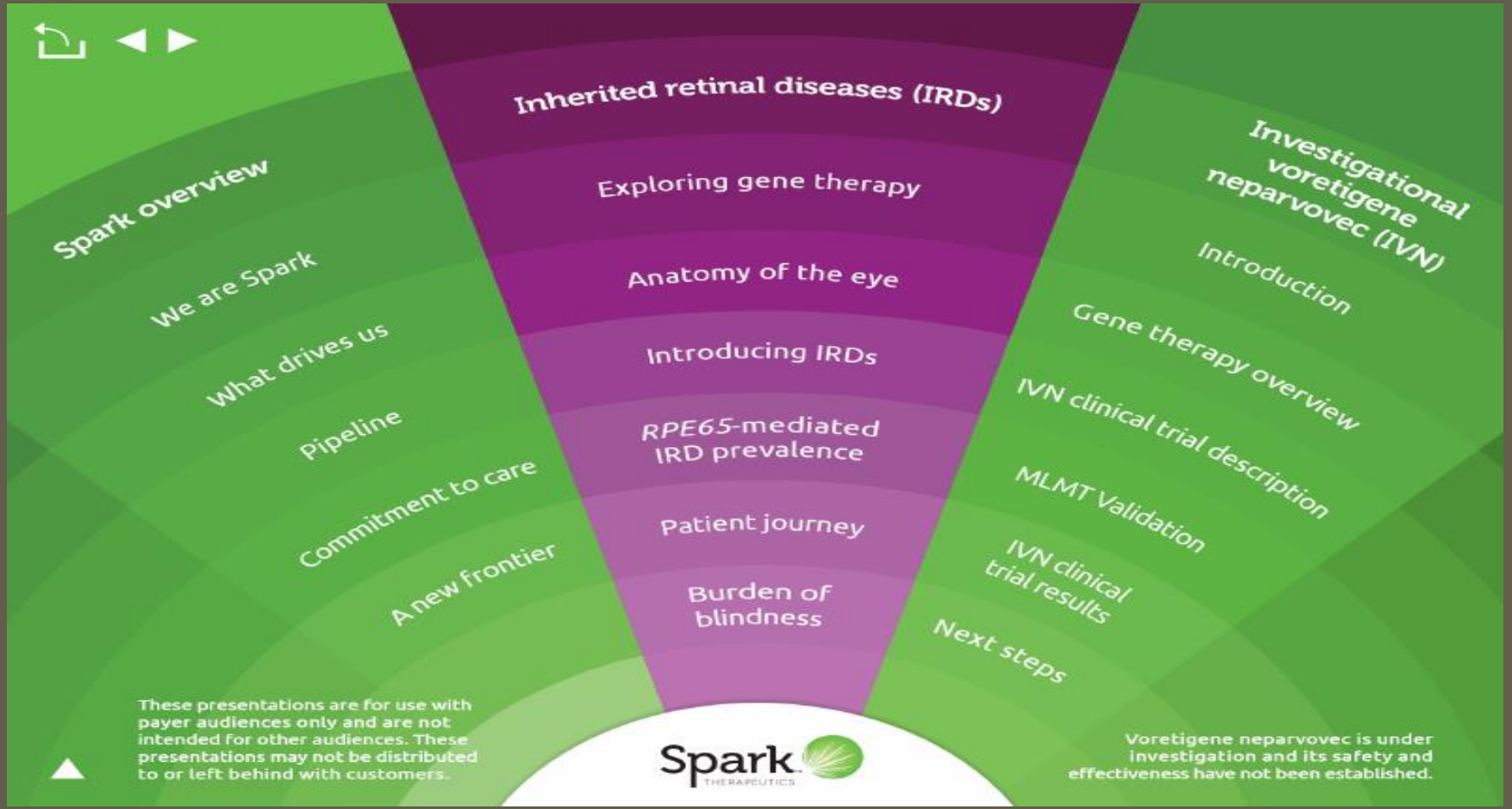
Product information (e.g., drug class, device description and features)
Indication sought: study protocol, endpoints and patient population being studied
Factual presentation of results (i.e., no safety/efficacy characterization or conclusions)

Product-related programs or services (e.g., patient support programs)

Anticipated timeline for possible FDA approval/clearance

Pricing information

Patient utilization projections (epidemiology data projection on incidence and prevalence)



Representative slides; not the entire presentation

Representative slides; not the entire presentation

Spark Therapeutics is a fully integrated gene therapy company

We don't follow footsteps—we create the path

Investigational voretigene neparvovec (IVN) has orphan designations in the United States and European Union, as well as breakthrough therapy designation in the United States[1]

Reference

Spark THERAPEUTICS

Representative slides; not the entire presentation

Spark Therapeutics is a fully integrated gene therapy company

We don't follow footsteps—we create the path

Gene therapy research targets

Viral vector platforms

Our most advanced product candidate is **investigational voretigene neparvovec (IVN),** a potential therapy for patients with vision loss due to confirmed biallelic *RPE65* mutation-associated retinal dystrophy[1]

Investigational voretigene neparvovec (IVN) has orphan designations in the United States and European Union, as well as breakthrough therapy designation in the United States[1]

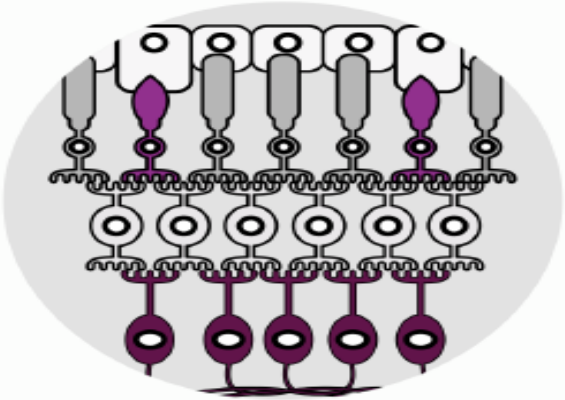
Reference

Spark THERAPEUTICS

Representative slides; not the entire presentation

Biallelic *RPE65*-mediated IRD

RPE65 gene encodes the RPE65 protein, a critical component in the visual cycle[1]



- The RPE65 protein affects the function of both rods and cones, but its greatest initial impact is rod-mediated[2]
- The RPE65 protein aids in converting light that enters the eye into electrical signals that go to the brain[1]
- Mutations to the *RPE65* gene impact the visual cycle[3]
- *RPE65* mutations disturb function of the RPE65 protein, leading to photoreceptor degeneration and progressive vision loss[3]
- In severe cases, *RPE65* mutations manifest as visual impairment at birth[1]

References

Spark THERAPEUTICS

Representative slides; not the entire presentation

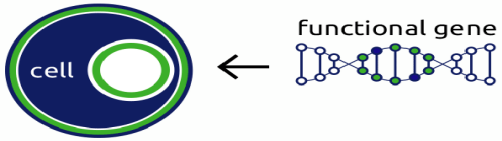
Approaches to treating genetic disease

The goal of gene therapy research is to employ new genetic material to address a defective genetic sequence[1]

Gene therapy approaches may:

Introduce

a new gene into the body to help fight disease[1]



Gene therapies are being investigated to determine whether they can help the body compensate for a disease-causing copy of a gene and potentially alter the effect of the disease[2-4]

References

Spark THERAPEUTICS

Representative slides; not the entire presentation

The development of IVN

IVN has completed the randomized, controlled, pivotal portion of the phase 3 clinical trial for potential treatment of *RPE65*-mediated IRD[1]

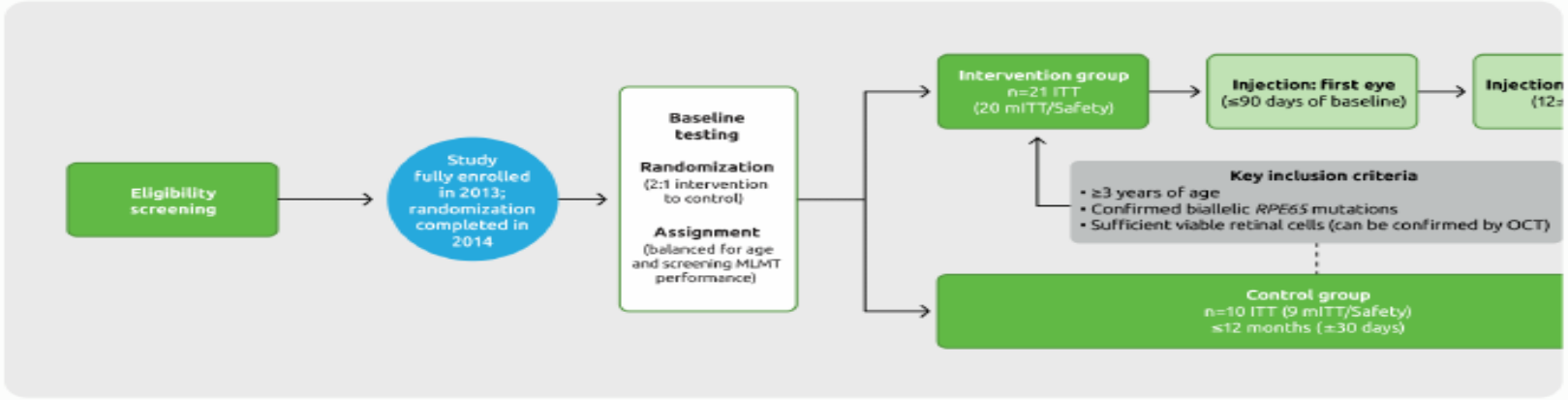
Voretigene neparvovec is under investigation and its safety and effectiveness have not been established.

References

Spark THERAPEUTICS

Representative slides; not the entire presentation

Phase 3 clinical trial design[1]



The intent-to-treat (ITT) population included all randomized subjects and the modified ITT (mITT) population included all randomized subjects who did not withdraw, or were not withdrawn, prior to any of the following people knowing the treatment assignment: the subject, parent, principal investigator, or medical monitor.

MLMT, multi-luminance mobility testing; OCT, optical coherence tomography; vg, vector genomes.

Phase 3 baseline demographics

Reference

Spark THERAPEUTICS

Representative slides; not the entire presentation

PRIMARY ENDPOINT

Bilateral multi-luminance mobility test

Measures functional vision at light levels encountered during typical activities of daily living[1,2]

Refers to participants' ability (speed and accuracy) to navigate a mobility course under a variety of specified light levels[1,2]

While taking the test, each subject follows arrows on the floor, steps over objects in their path, and exits the course[1,2]

Light levels are measured by lux[1]

References

1. Russell SR, Bennet J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with *RPE65*-mediated inherited retinal dystrophy: a randomized, controlled, open-label, phase 3 trial. *The Lancet*. 2017;389:1-28. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31868-8/. Accessed August 18, 2017. **2.** Chung D, McCague S, Yu Z, et al. Novel mobility test to assess functional vision in patients with inherited retinal dystrophies. *Clin Exp Ophthalmol*. August 31, 2017.

Representative slides; not the entire presentation

Overview of phase 3 one-year results: efficacy endpoints (ITT)[1,2]

Assessment	Measurement	Difference (95% CI) Intervention-control	Statistical significance (*P*-value)
Primary endpoint MLMT performance	Bilateral, change score	1.6 (0.72, 2.41)	$p = 0.001$
Secondary endpoints FST testing	Monocular, averaged over both eyes, log10 (cd.s/m^2)	-2.11 (-3.19, -1.04)	$p < 0.001$
MLMT performance	Assigned first eye, change score	1.7 (0.89, 2.52)	$p = 0.001$
Visual acuity	Monocular, averaged over both eyes, LogMAR† (Holladay)	-0.16 (-0.41, 0.08)	$p = 0.17$
Additional endpoint Visual field	Goldmann III4e sum total degrees, monocular, averaged over both eyes	378.7 (145.5, 612.0)	Nominal $p = 0.006$
	Humphrey macula threshold, dB, monocular, averaged over both eyes	7.9 (3.5, 12.2)	Nominal $p < 0.001$

dB, decibel; FST, full-field light sensitivity threshold; ITT, intent-to-treat; MLMT, multi-luminance mobility test.
†LogMAR assigned using scale adapted from Holladay et al.

Voretigene neparvovec is under investigation and its safety and effectiveness have not been established.

References

Spark THERAPEUTICS

Representative slides; not the entire presentation

Phase 3 safety overview years 1 and 2

No product-related serious adverse events or deleterious immune responses[1]

- All subjects experienced at least one treatment emergent adverse event (TEAE)[1]
- No TEAEs were considered related to study drug[1]

Summary of TEAEs reported in more than one subject (safety)[1]

MedDRA system organ class/ preferred term	Intervention (N=20)	Control (N=9)	Overall (N=29)
Gastrointestinal disorders	12 (60%)	3 (33%)	15 (52%)
Vomiting	8 (40%)	2 (22%)	10 (34%)
Nausea	6 (30%)	1 (11%)	7 (24%)
Diarrhea	2 (10%)	1 (11%)	3 (10%)
Upper abdominal pain	2 (10%)	0	2 (7%)
Nervous system disorders	10 (50%)	3 (33%)	13 (45%)
Headache	7 (35%)	2 (22%)	9 (31%)
Eye disorders	10 (50%)	1 (11%)	11 (38%)
Cataract	3 (15%)	0	3 (10%)
Eye inflammation	2 (10%)	0	2 (7%)
Retinal tear	2 (10%)	0	2 (7%)

For system organ class (SOC), N (%) includes any subject with an AE in that SOC; listed preferred terms (PTs) only include those experienced by more than one subject overall.

Voretigene neparvovec is under investigation and its safety and effectiveness have not been established.

Reference

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COMMUNICATIONS TO PAYORS REGARDING INVESTIGATIONAL DRUGS AND DEVICES

Perspectives on Implementing the Guidance

- Novel considerations by firms engaging in these communications: Who should deliver? Who else can be present? Who should create? Who should review and approve?
- Critical for training of representatives delivering information to emphasize key differences from traditional product promotion (e.g., no characterization or conclusions of efficacy/safety, prominent mention of investigational status)
- Must resist temptation for firms to answer "So what?" question by payor after hearing all the investigational data
- Providing recommended data and status updates: mode of dissemination, optional vs necessary updates, positive and negative developments
- Discontinue use of these communications upon FDA approval

COMMUNICATIONS TO PAYORS REGARDING INVESTIGATIONAL DRUGS AND DEVICES

Perspectives on Implementing the Guidance (continued)

- Guidance has been positively received by payors, especially for investigational products with unique coverage or reimbursement considerations
- May be particularly useful for companies introducing novel therapies or first in class therapies
- Payors appreciate that information is factual and objective; not promotional in tone or intent
- Payors receive information that previously would require unsolicited inquiries via Medical Information, through AMCP dossier submissions or at medical/scientific conferences

Payor Perspective on 2018 Promotional Guidance

S. Jay Weaver, PharmD, MPH
AVP, Pharmaceutical Care Strategy
HCSC

Payor needs for technology evaluation/evidence

* Pharmacy and Therapeutics Committee (P&T)
  * Clinical committee assesses clinical merits and place-in-care
  * Traditionally used published studies, labeling/PI, clinical guidelines

* Contracting/Business Committee
  * Evaluated placement of products relative to P&T mandate
  * Traditionally use home-grown HCEI models, published evaluations and limited manufacturer models for financial considerations
  * ICER and NICE evaluations emerging as additional data points

Traditional payor budgeting process and tools

HEOR models (HCEI)

* Budget-impact models
* Epidemiology data
* Enrollment projections

Pipeline evaluation and projection

* Pink Sheet
* FDA
* Investor calls
* Pricing (best guess)

Challenges

* Assumption variability
* Timeliness of information
* Costliness of research
* Price of publications
* Lack of outcomes data (surrogate endpoint only)
* Small populations for orphan products

Key points of “The Guidance”

* Changed from “substantial evidence” (typically two randomized controlled trials) to “competent and reliable scientific evidence”, if these claims were made to “formulary committees and similar entities” and “directly-related to approved indications.”
* Allows for sharing information regarding unapproved products to payors as long as that information is “unbiased, factual, accurate, and non-misleading, and are presented with statements regarding:
  * Approval status
  * Stage of product development
  * Material aspects of study design (where appropriate)
  * Approved indication if discussing indication for which it is not approved

Impact

Wins

* Allows payors to see more appropriate models to address financial questions
* Earlier budget impact evaluations with less plan overhead

Concerns

* Declining evidentiary standards requiring more vigilance
* Unclear if changing evidentiary standards for manufacturers translates to pricing improvements

Life after “The Guidance” around the payor community

* Increased offers to discuss pipeline/investigational agents
* Expanded discussions of HCEI models
* Offers to meet to discuss agents prior to launch
* Payors reconfiguring evaluation techniques to include PROs
* Payors contemplating how to leverage their data-sets in partnership with industry

Questions

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