Planning for the 2019 Specialty Drug Spend

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Disclosure for Nicole Trask

I have no actual or potential conflict of interest in relation to this presentation.

Objectives

- Identify high-impact specialty pipeline drugs expected to reach the market in 2019-2020
- Summarize efficacy data for high-impact specialty pipeline drugs and indicate their anticipated place in therapy
- Compare specialty pipeline drugs to currently available therapeutic options
- Predict the budgetary impact of specialty pipeline drugs and discuss strategies to mitigate costs

Identifying High-Impact Drugs

Two key drivers

- Clinical impact
  - Efficacy/effectiveness
  - Therapeutic alternatives
- Economic impact
  - Cost
  - Volume

Assessing Clinical Impact

Clinical trial data

- Placebo-controlled, head-to-head studies
- Adverse events
- Potential drug-drug interactions
- Target population
- Patient willingness to use medication

Therapeutic alternatives

- Me-too drug vs. first-in-class
- Market competition
- Consensus guidelines

Assessing Economic Impact

Cost

- NADAC, AWP, WAC
- Supplemental rebate
- Outcomes-based contracts
- Value assessments (e.g., AHRQ, ICER, PCORI)

Volume

- Prevalence/incidence of disease
- Frequency of administration
- Duration of therapy

AHRQ=Agency for Healthcare Research and Quality, AWP=average wholesale price, ICER=Institute for Clinical and Economic Review, NADAC=national average drug acquisition cost, PCORI=Patient-centered Outcomes Research Institute, WAC=wholesale acquisition cost

Other Factors Affecting Budget Impact

Disease-specific

- Chronic vs. fatal disease
- Disease progression
- Ease of diagnosis (e.g., need for additional testing)

Prescriber-specific

- Availability of relevant prescriber specialty
- Requirement for additional training for drug administration

Assessing Budget Impact

- **Proactive pharmaceutical pipeline monitoring**
  - Focus on high-cost disease states, specialty drugs (e.g., gene therapy, CAR-T therapy, orphan diseases)
- **Budget impact analysis completed for drugs with potentially high clinical *and* economic impact**
  - Pharmacy and/or medical claims to evaluate prevalence
  - Estimate market share, uptake
  - Cost – net cost; consider shifting in utilization patterns

CAR-T=chimeric antigen receptor-T

Lessons Learned

Difficult to predict uptake of new drugs

- Skepticism surrounding safety/efficacy
- Clinical inertia, lack of consensus guideline updates
- Relative cost
- Logistics surrounding drug delivery

Updates to process

- Project run rate – utilization patterns over time
  - Incidence, prevalence
  - Cure vs. chronic therapy

HIGH-IMPACT PIPELINE DRUGS

Hemophilia A[1,2]

Clinical features

- X-linked bleeding disorder caused by mutations in gene encoding coagulation factor VIII
- Severe disease associated with spontaneous or provoked bleeding in joints/soft tissue and increased risk of intracranial hemorrhage, early death

Incidence/Prevalence

- Affects 1 in 5,000 male births
- Approximately 400 infants born with hemophilia A annually
- Prevalence of hemophilia unknown; approximately ~20,000

Valoctocogene Roxaparvovec[1,3]

- **Proposed indication:** Treatment of hemophilia A
- **MOA:** AAV5-factor VIII vector
  - Contains codon-optimized expression cassette for the SQ variant of B-domain-deleted human factor VIII
  - Restoration of the missing gene needed to produce endogenous factor VIII
  - Given as single IV infusion

AAV2=adeno-associated virus type 5, IV=intravenous, MOA=mechanism of action

Valoctocogene Roxaparvovec: Clinical Data[1]

Phase I/II data: Design

- Open-label, dose-escalation
- Population: N=9; adult men with severe hemophilia A
- Intervention: One-time IV administration at low (n=1), intermediate (n=1), or high dose (n=7)
- Primary outcome: Safety

Valoctocogene Roxaparvovec: Clinical Data[1]

Phase I/II data: Safety results

Adverse Event	Mild	Moderate	Severe
ALT elevation	n=7	-	-
Arthralgia	n=5	n=1	-
AST elevation	n=2	n=1	-
Back pain	n=4	-	-
Fatigue	n=3	-	-
Productive cough	n=3	-	-
Chronic arthropathy progression	-	-	n=1

ALT=alanine aminotransferase, AST=aspartate aminotransferase

Valoctocogene Roxaparvovec: Clinical Data[1]

Phase I/II data: Efficacy results

- **High-dose cohort:**
  - Factor VIII activity ≥50 IU/dL achieved by week 20
  - Median factor VIII activity at week 52: 77 IU/dL
  - In patients who received factor VIII prophylaxis prior to study (n=6), median ABR decreased from 16 events/year to 1 event/year
  - Median consumption of factor VIII decreased from 5,286 to 65 IU/kg/year
  - Five patients discontinued exogenous factor VIII administration

ABR=annualized bleeding rate

Valoctocogene Roxaparvovec: Clinical Impact[1,4,5]

Therapeutic alternatives

- Factor VIII concentrate is current standard of care
  - On-demand treatment of active bleeding episodes
  - Prophylactic administration of factor VIII concentrate recommended in severe hemophilia
  - Products with longer half-lives preferred due to less-frequent administration
- Treatment is generally life-long, associated with significant costs

Valoctocogene Roxaparvovec: Clinical Impact[6-8]

Hemophilia pipeline

- Fitusiran
  - RNAi therapeutic for treatment of hemophilia A or B
  - Phase II OLE study (N=33):
    - Treatment resulted in increases in thrombin, decreases in antithrombin
    - Median follow-up of 11 months: 48% of patients had no bleeds
  - Phase III ATLAS program resumed after FDA hold was lifted – risk mitigation measures include reduced doses of factor replacement, bypassing agents for breakthrough bleeds

FDA=Food and Drug Administration, OLE=open-label extension, RNAi=ribonucleic acid interference

Valoctocogene Roxaparvovec: Clinical Impact[1,3,9]

Potential Advantages

- Requires a single IV administration
- May significantly reduce factor consumption or provide possible cure
- Has the potential to significantly reduce health care costs over time

Potential Disadvantages

- Likely to be associated with extremely high upfront costs
- May require administration through specialized treatment centers
- Clinical trial data suggests factor VIII levels may decline over time

Valoctocogene Roxaparvovec: Economic Impact[10,11]

Cost

- Cost data not yet available
  - Analysts' cost predictions range from $1 to $2 million
- Potential long-term cost savings should be considered
  - High upfront costs may be offset by reduced factor VIII consumption
- Innovative payment strategies
  - Pay for performance
  - "Annuity" payments

Valoctocogene Roxaparvovec: Economic Impact[1,2]

Volume

- Incidence/prevalence
  - Affects 1 in 5,000 male births
  - Prevalence estimated to be 1 in 12,000
- Duration: one-time administration
- Other key facts
  - Manufacturing facility has the capacity to support ~2,000 patients per year

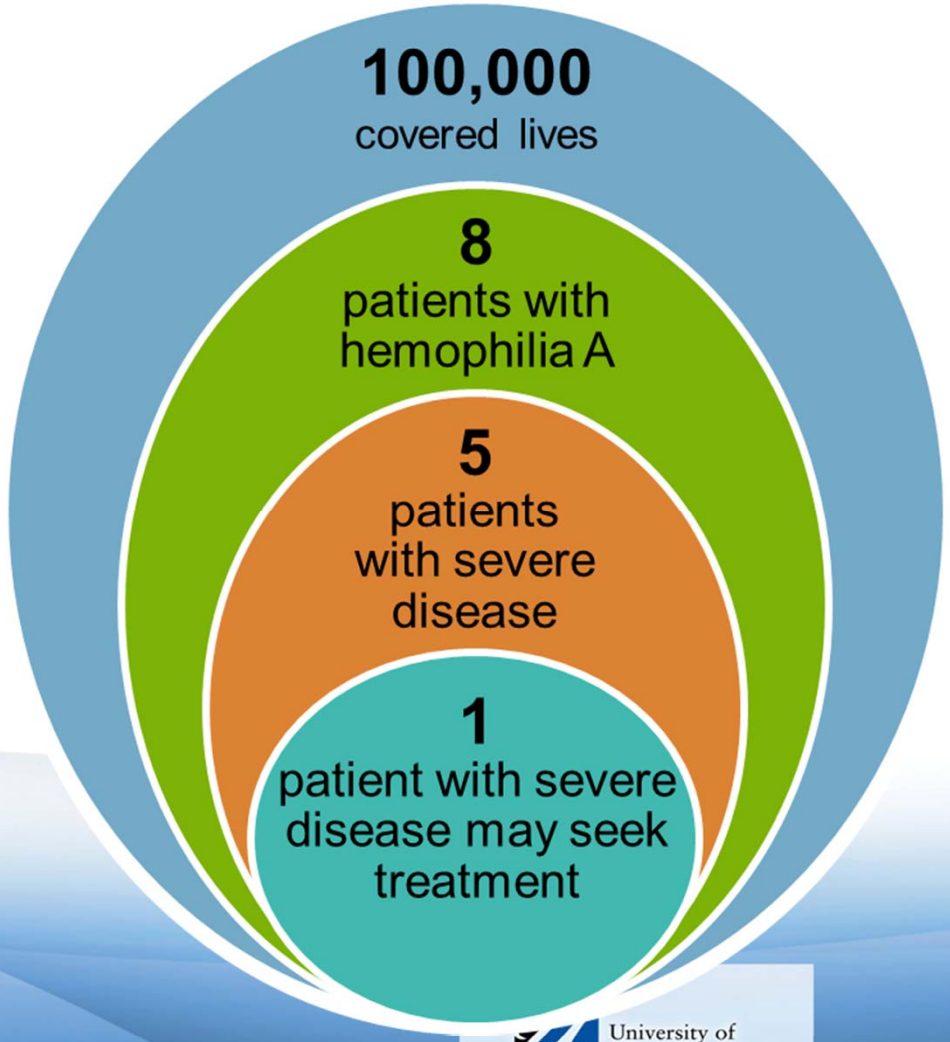
Valoctocogene Roxaparvovec: Budget Impact[12,13]

Commercial plan

- Approximately $1.5 million/patient for treatment
- **$1.5 million/year**

Timeline

- Two Phase III studies currently ongoing
- Breakthrough Therapy, Orphan Drug designations



NTRK Gene Fusion[14,15]

Clinical features

- NTRK genes encode TRK family of NTRK receptors; involved in the growth, differentiation, and survival of neurons
- NTRK gene fusions implicated in a broad range of malignancies

Prevalence

- NTRK gene fusions are implicated in ~1% of all solid tumors, regardless of tissue of origin

NTRK=neurotrophic receptor tyrosine kinase, TRK=tropomyosin receptor kinase

Larotrectinib[16,17]

- **Proposed indication:** Treatment of locally advanced or metastatic solid tumors harboring an NTRK gene fusion
- **MOA:** Pan-TRK inhibitor
  - Tumor-agnostic; targets tumor based on presence of NTRK gene fusion and not tissue type
  - Tumor-profiling diagnostic also in development; broad scope that would screen for several tumor markers

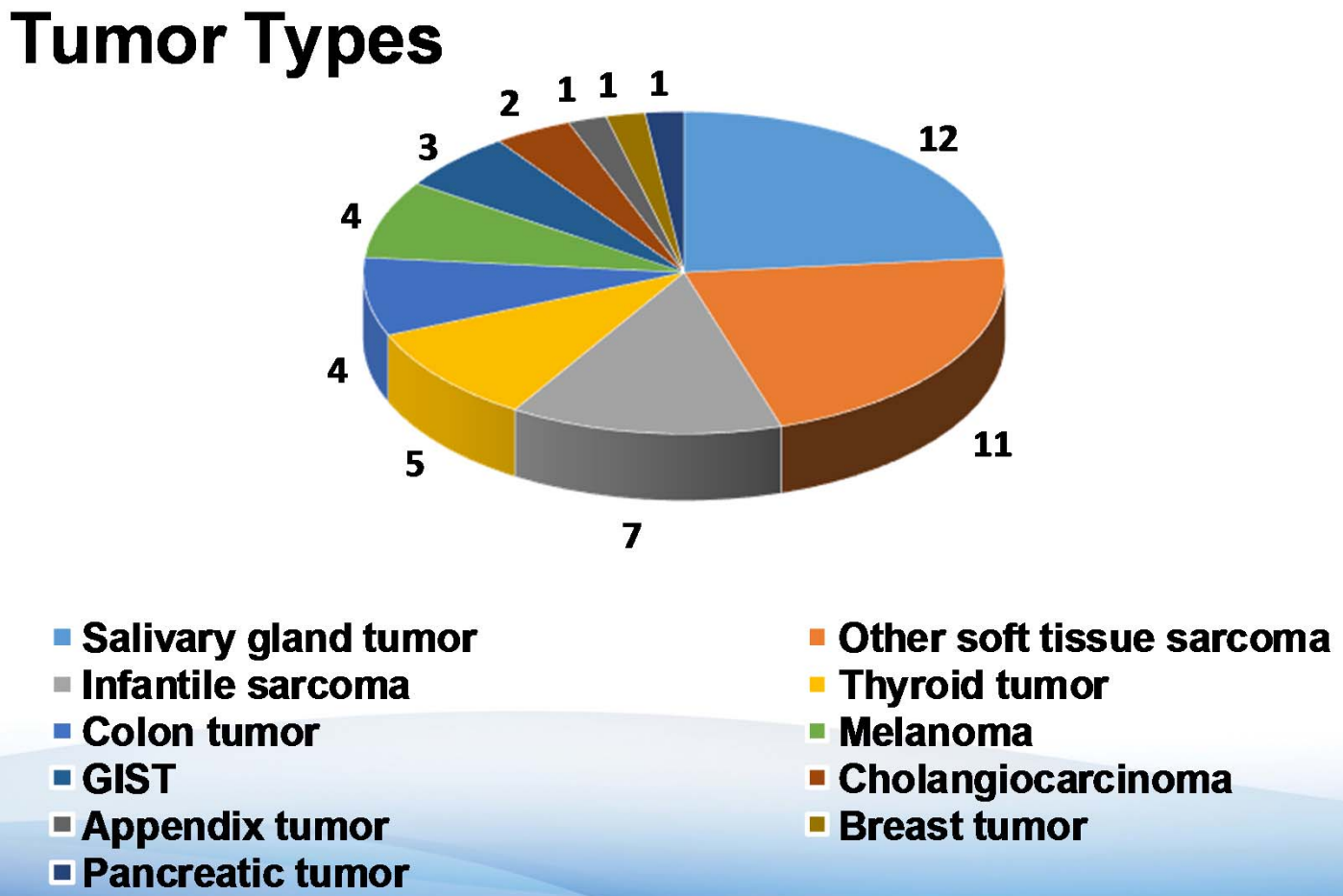
Larotrectinib: Clinical Data[15]

Phase II trial: Design

- Open-label, dose-escalation
- Population: N=55; adults and adolescents with TRK fusion-positive tumors
- Intervention: larotrectinib 100 mg orally twice daily* until disease progression
- Primary outcome: ORR

*For patients with body surface area ≥1 m^2
ORR=overall response rate

Larotrectinib: Clinical Data[15]



GIST=gastrointestinal stromal tumor

Larotrectinib: Clinical Data[15,18]

Phase II trial: Results

- ORR:
  - Independent review: 75% (95% CI, 61 to 85)
  - Investigator assessment: 80% (95% CI, 67 to 90)
- At 1 year:
  - 71% of responses were ongoing
  - 55% of patients had no disease progression
- At 9 months, 86% of patients who responded continued treatment or had surgery with curative intent

CI=confidence interval

Larotrectinib: Clinical Data[17,18]

Therapeutic alternatives

- Standard of care therapy varies based on tumor type, presence of other biomarkers
- Chemotherapy
- Surgery

Larotrectinib: Clinical Impact[16,19,20]

NTRK gene fusion pipeline

- Entrectinib
  - Treatment of NTRK-positive, locally-advanced or metastatic solid tumors
  - Phase I data (N=24):

    79% of patients with solid tumors positive for NTRK, ROS-1, or ALK rearrangements achieved objective responses
  - Breakthrough Therapy designation
  - Phase II studies currently ongoing

Larotrectinib: Clinical Impact[16,21,22]

Potential Advantages

- May effectively target cancer based on presence of biomarker
- May provide effective treatment option in rare, difficult-to-treat cancer types
- Being developed in liquid form for pediatric use

Potential Disadvantages

- Acquired resistance occurred in patients who initially responded and then progressed
- NTRK gene fusions very rare; limited data for each tumor type
- Genetic testing needed to identify treatment candidates

Larotrectinib: Economic Impact[21]

Cost

- Cost data not yet available
  - Analysts' cost projections ~$180,000 per patient
  - Genetic testing for NTRK gene fusion would need to be done for all tumor types - $1,000 to $1,500 per patient
- Outcomes-based contracts – survival benefit, durability of response

Larotrectinib: Economic Impact[23]

Volume

- Prevalence: 1,500 to 5,000 patients in the US
  - NTRK gene fusions are present in ~1% of all solid tumors
- Duration: variable; treatment continues until disease progression, remission, or surgery with curative intent

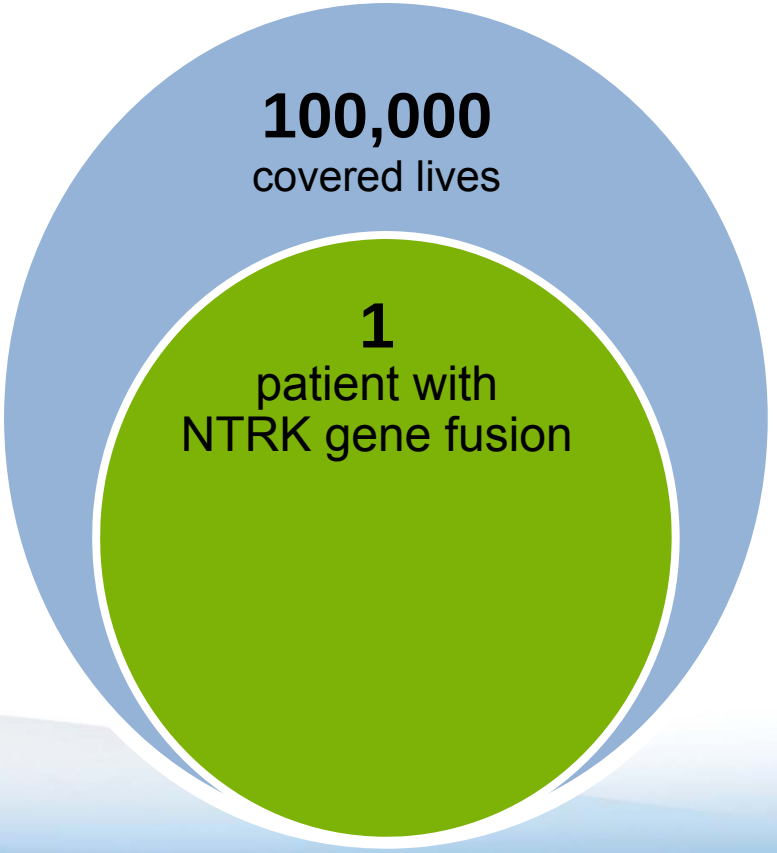
Larotrectinib: Budget Impact[16,24]

Commercial plan

- Approximately $180,000/year for treatment
- **$180,000/year**

Timeline

- FDA decision expected 11/26/2018
- Breakthrough Therapy, Rare Pediatric Disease, Orphan Drug, Priority Review designations



Cerebral Adrenoleukodystrophy (cALD)[25-27]

Clinical features

- X-linked neurodegenerative disease primarily affecting males
- Caused by mutations in ABCD1 gene → loss of function in ALD protein
- Progressive destruction of myelin sheath surrounding nerves
- Loss of neurologic function, death

Incidence

- Approximately 1 in 20,000 to 50,000 births

ABCD1=ATP-binding cassette, subfamily D, member 1, ALD=adrenoleukodystrophy

Elivaldogene tavalentivec[25,26,28]

- **Proposed indication:** Treatment of childhood cALD
- **MOA:** Lentiviral vector containing ABCD1 cDNA
  - Patient's own CD34+ hematopoietic stem cells transduced *ex vivo*
  - Stem cells proliferate *in vivo*; some cells travel to brain and differentiate into microglial cells
  - Expressed ABCD1 restores function of ALD protein
  - Administered as single IV infusion

cDNA=complimentary DNA

Elivaldogene tavalentivec: Clinical Data[25,29,30]

Phase II/III Starbeam study: Design

- Single-arm, open-label
- Population: N=17; boys with early-stage cALD
- Intervention: Single IV infusion of elivaldogene tavalentivec following myeloablative conditioning
- Primary outcomes: Proportion of patients alive and with no MFDs at 24 months

MFDs=major functional disabilities

Elivaldogene tavalentivec: Clinical Data[25,30]

Phase II/III Starbeam study: Interim results

- At 24 months post-infusion or discontinuation:
  - 15/17 subjects (88%) were alive and free of MFDs (95% CI, 64 to 99%)
  - 17/17 subjects were able to express functional ALD protein
  - Median follow-up: 29.4 months (range, 21.6 to 42.0 months)
  - No incidence of engraftment failure, GVHD, or life-threatening infection
  - No incidence of insertional oncogenesis

GVHD=graft-versus-host disease

Elivaldogene tavalentivec: Clinical Impact[27,31]

Therapeutic alternatives

- Allogeneic hematopoietic stem cell transplant is the only effective treatment
  - Most effective at early stage of neurodegeneration
  - May take months to have therapeutic effect
- Corticosteroid therapy for symptomatic treatment of abnormal adrenal function

Elivaldogene tavalentivec: Clinical Impact[25,31,32]

Potential Advantages

- Using patient's own stem cells avoids challenges of finding matched sibling donor which can prevent/delay treatment
- May provide life-saving treatment for disease that is typically fatal by age 10

Potential Disadvantages

- Longer-term data needed to evaluate durability of response

Elivaldogene tavalentivec: Economic Impact[25]

Cost

- Cost data not available
  - May be similar in cost to other gene therapies in development – $1 to $1.5 million per patient
- Outcomes-based contracts – survival benefit, durability of response

Elivaldogene tavalentivec: Economic Impact[25-27]

Volume

- Incidence: 1 in 20,000 to 50,000 births
- Duration: one-time administration
- Other key facts
  - Newborn screening for ALD was added to RUSP in February 2016 but has not been fully-implemented in all states

ALD=adrenoleukodystrophy, RUSP=Recommended Universal Screening Panel

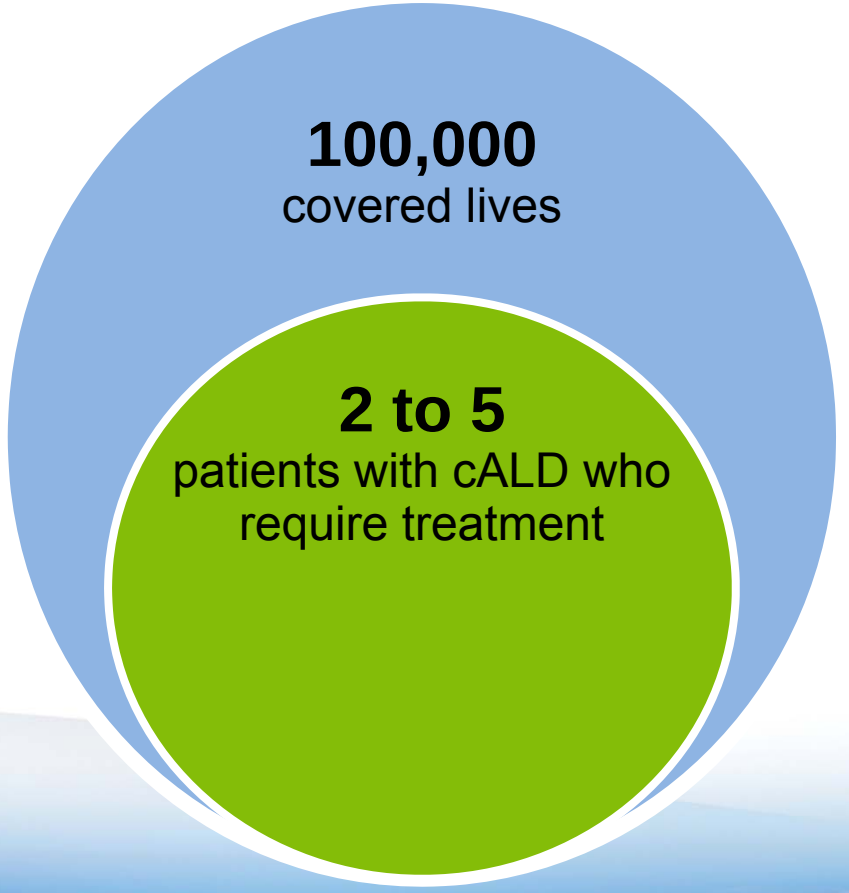
Elivaldogene tavalentivec: Budget Impact[25-28,32]

Commercial plan

- Approximately $1 million/patient for treatment
- **$2 to $5 million/year**

Timeline

- Final data collection for Starbeam study expected 8/2019
- Breakthrough Therapy designation



Complete DiGeorge Anomaly[33]

Clinical features

- Individuals are born without a thymus, resulting in lack of functional T cells → severe immunodeficiency
- Untreated disease is uniformly fatal, with death typically occurring in first 24 months of life

Incidence

- 1 in 300,000 infants
- Affects 10 to 20 infants born in US each year

RVT-802[33,34]

- **Proposed indication:** treatment of primary immune deficiency associated with complete DiGeorge anomaly
- **MOA:** tissue-based regenerative therapy
  - Uses proprietary processes to harvest, culture, and apply allogeneic thymic tissue
  - Does not correct underlying defects in chromosome 22 responsible for complete DiGeorge anomaly
  - One-time administration

RVT-802: Clinical Impact[34]

Clinical trial data (N=60):

- Survival rate >70%
- Of 43 patients alive at time of publication: median survival, 4.7 years (range, 6 months to 16 years)
- Naïve T cells developed within 3 to 5 months post-transplantation
- Recipients were able to discontinue antibiotic prophylaxis and immunoglobulin replacement

RVT-802: Clinical Impact[34,35]

Therapeutic alternatives

- Protective isolation
- Hematopoietic stem cell transplant
  - Increased T cells secondary to expansion of donor memory T cells, not generation of naïve T cells → does not restore full T cell functionality
- Management of opportunistic infections

RVT-802: Clinical Impact[33-35]

Potential Advantages

- May provide a significant survival benefit for a uniformly-fatal disease
- Unlike current treatment options, RVT-802 allows patients to produce fully functional T cell population

Potential Disadvantages

- Does not correct underlying defects in chromosome 22 that cause disease
- Availability of therapy may be limited

RVT-802: Economic Impact[36]

Cost

- Cost data not available
  - Extremely rare disease and one-time administration
  - May be similar in cost to gene therapies for rare disease – $1 to $1.5 million per patient
- Outcomes-based contracts – manufacturer expressed interest in outcomes-based contracting with payment contingent on survival

RVT-802: Economic Impact[34,36]

Volume

- Incidence: 1 in 300,000 infants
  - 10 to 20 children born in the US annually
- Duration: one-time administration
- Other key facts
  - Availability of RVT-802 is dependent on availability of donor thymic tissue and treatment centers

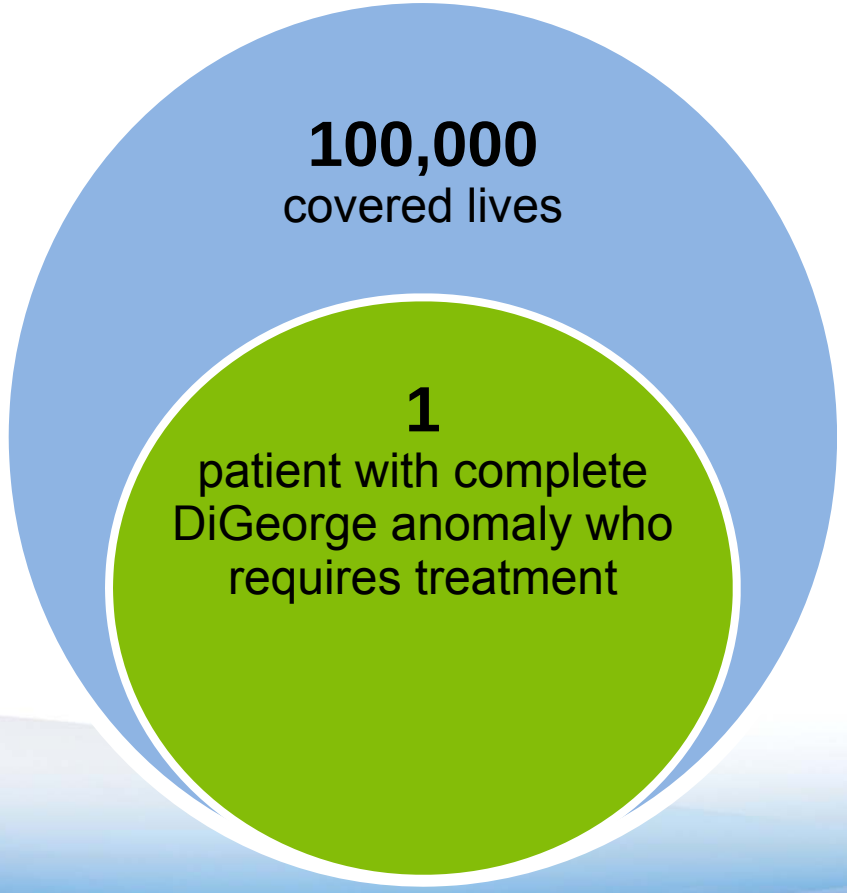
RVT-802: Budget Impact[33,37-39]

Commercial plan

- Approximately $1.5 million/patient for treatment
- **$1.5 million/year**

Timeline

- Rolling BLA submission to be completed by end of 2018
- Breakthrough Therapy, RMAT, Orphan Disease, Pediatric Rare Disease designations



BLA=Biologics License Application, RMAT=Regenerative Medicine Advanced Therapy

Hairy Cell Leukemia[40]

Clinical features

- Rare, slow-growing, incurable leukemia
- Characterized by overproduction of abnormal B cells or lymphocytes by the bone marrow
- Patients may also experience infections, bleeding, and anemia

Incidence

- Approximately 1,000 individuals diagnosed in US annually

Moxetumomab Pasudotox[41]

- **Proposed indication:** relapsed or refractory hairy cell leukemia in patients who received ≥2 prior lines of therapy
- **MOA:** anti-CD22 recombinant immunotoxin
  - Contains binding portion of anti-CD22 antibody to target drug delivery while toxin portion kills the targeted cancer cells

Moxetumomab Pasudotox: Clinical Impact[41,42]

Phase III 1053 trial: Design

- Single-arm, multicenter
- Population: N=80; adults with relapsed or refractory hairy cell leukemia who have received ≥2 prior lines of therapy
- Intervention: moxetumomab pasudotox IV on days 1, 3, and 5 of each 28 day cycle for max of 6 cycles or until disease progression
- Primary outcomes: rate of durable CR*

*Durable CR=complete response with hematologic remission for >180 days
Hematologic remission=neutrophils ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L, hemoglobin ≥11 g/dL, no transfusions/growth factor for at least 4 weeks
CR=complete response

Moxetumomab Pasudotox: Clinical Impact[40,41]

Phase III 1053 trial: Interim results

- Primary endpoint of rate of durable CR was met
  - Durable CR: 30%
  - ORR: 75%
  - CR rate: 41%
    - MRD negative status*: 82% of patients with CR

*Complete response with immunohistochemistry MRD negativity
MRD=minimal residual disease, ORR=objective response rate

Moxetumomab Pasudotox: Clinical Impact[43]

Therapeutic alternatives

- **Initial treatment**
  - Chemotherapy (purine analogs [e.g., cladribine, pentostatin]
- **First relapse**
  - Clinical trial
  - Rituximab ± purine analog
  - Interferon alpha
- **Subsequent relapse**
  - Clinical trial
  - Vemurafenib ± rituximab
  - Ibrutinib

Moxetumomab Pasudotox: Clinical Impact[40,42,44]

Potential Advantages

- May provide an effective treatment option for refractory disease
- Phase III trial demonstrated durability of response >180 days
- If approved, would be first-in-class immunotoxin

Potential Disadvantages

- PFS data is not yet available
- Overall survival not evaluated in Phase III trial
- Highly immunogenic in early studies

PFS=progression-free survival

Moxetumomab Pasudotox: Economic Impact[45]

Cost

- Cost data not available
  - Based on industry analysts' US sales projections and incidence of refractory disease, may cost ~$300,000 per patient
- Outcomes-based contracts – survival benefit, durability of response

Moxetumomab Pasudotox: Economic Impact[24,41,42,46]

Volume

- Incidence: 1,000 new cases diagnosed annually in US; 40% of disease is refractory
- Duration: variable; treatment continues until disease progression or max of 6 cycles*
- Other key facts
  - Also being studied in relapsed/refractory B-cell ALL

*Based on Phase III study
ALL=acute lymphoblastic leukemia

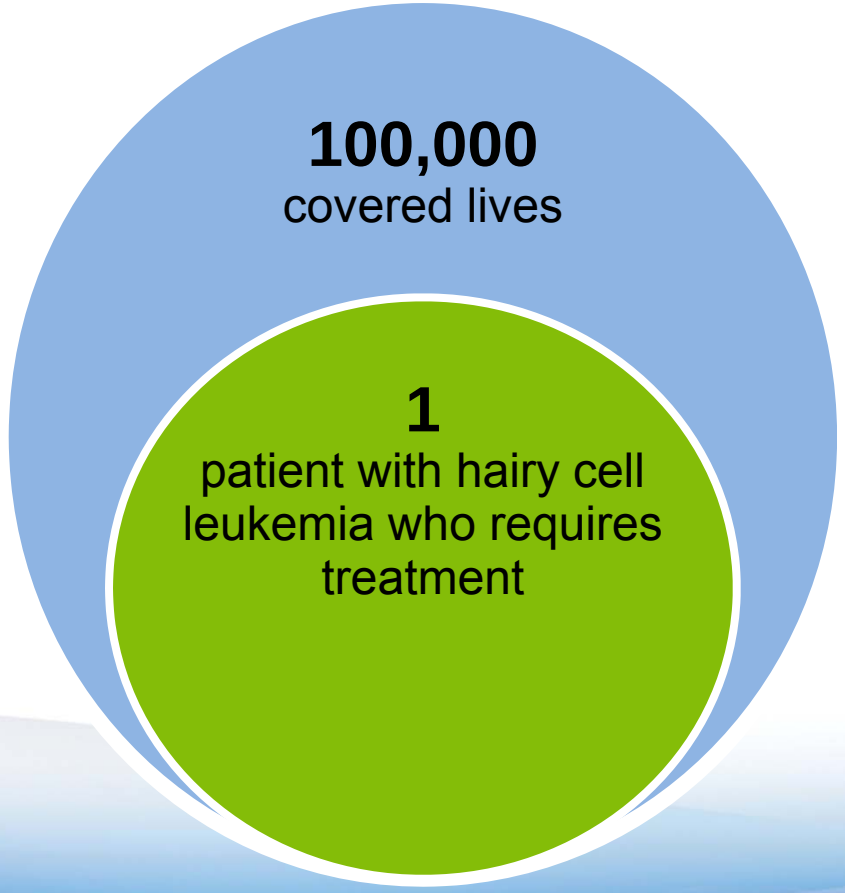
Moxetumomab Pasudotox: Budget Impact[40,41,45]

Commercial plan

- Approximately $300,000/year for treatment
- **$300,000/year**

Timeline

- FDA decision expected Q3 2018
- Priority Review, Orphan Drug designations



Q3=third quarter

Conclusions

- Specialty pipeline agents may offer important therapeutic, safety advantages
- Approval of high-cost specialty therapies highlight need for innovative management strategies
- Proactive pipeline monitoring and a solid understanding of plan membership are key to anticipating budget impact of new drugs