Mezzion Pharmaceuticals

Shaping the future of single ventricle heart disease (SVHD)

July, 2018

Safe Harbor Statement

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A Specialty Pharmaceutical Development Company

- Mezzion Pharma Co., Ltd. is publicly-traded on Korea's KOSDAQ.
- Founded in 2002 jointly by Dong Hyun Park (Chairman & CEO of Mezzion) and Dong-A Pharmaceutical Co., Korea's largest pharmaceutical company, initially to develop udenafil in markets outside of Korea.
- Currently focused on the development and commercialization of udenafil for the treatment of single ventricle heart disease in patients that have undergone palliative surgery.
- A significant number of outside consultants with global pharma experience.
- An US entity, Mezzion Pharmaceuticals Inc. established in 2018 (currently, 2 operational offices in US).

Product and Indication

Udenafil for the Treatment of Single Ventricle Heart Disease (SVHD)

- Treatment of adolescents with single ventricle physiology after Fontan surgery
  - No approved medications specifically indicated for treatment of single ventricle heart disease
- Orphan Drug Status granted by US FDA in 2015 and by EMEA in 2016
- A multinational phase 3 clinical trial ongoing (US, Canada and Korea)
- Target NDA submission date in 2019 with accelerated review to be requested

Manufacturing

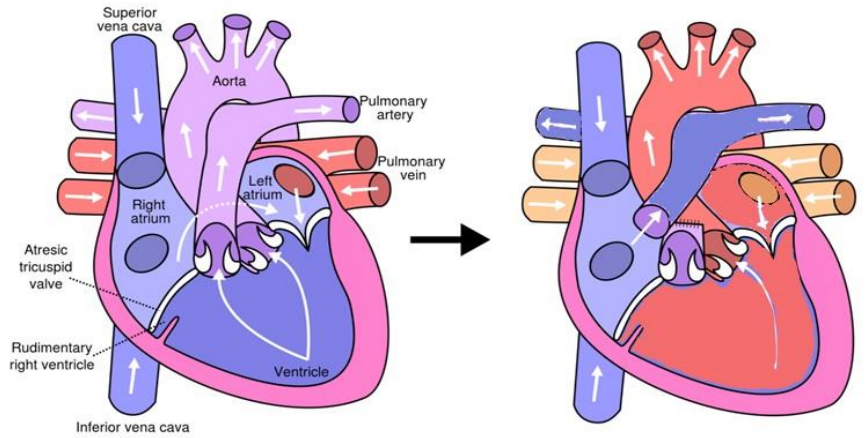
- **Reputable CMOs secured for manufacture of udenafil API and udenafil oral dosage form**

What is Fontan Procedure

The Fontan Procedure (FP) is a surgical intervention performed in children born with functional single-ventricle hearts, a congenital heart defect, who are not candidates for a two-ventricle repair.

FP consists of re-configuring the circulation to maximize the efficiency of a single ventricle

- "Fontan circulation" is achieved when the single ventricle is able to pump blood returning from the lungs to the body
- The blood returning from the body is able to travel to the lungs by direct blood vessel connections without the need of a pumping chamber



Hosein et al., 2007. Eur. J. Cardiothorac. Surg., 31, 344-353.; Ono et al., 2006. Eur. J Cardiothorac. Surg., 30, 923-929.

The goal of the FP is to separate the systemic and pulmonary circulations and to improve oxygen levels by redirecting venous blood directly to the lungs.
In turn, this creates two separate circulations and thereby decreases the workload of the heart.

Epidemiology

Single ventricular defect : Congenital defect in the heart with only one ventricle

- consists of about 1% of the total congenital heart defects
- Based on the US data, about 5.3 out of 10,000 is born with the single ventricular defect
- About 2,000 patients with the single ventricular defect are born every year in US

Fontan operation: the phase of a series of operations (total of 3 operations) in order to recover the function of the heart as normal as possible in the children with single ventricles

- The Fontan procedure is done during the age of 2~3, normally
- About 65% of the patients with single ventricles survive through the Fontan operation
- Around 1,270 new Fontan patients every year

At present, there are approximately 29,000 Fontan patients in US

Prognosis: Unmet medical needs

Patients that have undergone Fontan surgical palliation typically:

- Have a limited ability to augment pulmonary blood flow.
- Have limited systemic ventricle filling and therefore impaired preload.

These limitations are not adequately addressed by current heart failure therapies, which are directed primarily at contractility and afterload.

- ACE inhibitors, beta blockers, aldosterone antagonists, inotropic drugs do not address the primary pathophysiology associated with Fontan surgical palliation except cases of systemic ventricular systolic dysfunction.

Heart transplantation is an low probability option in Fontan palliated patients because:

- PVR is usually abnormally high.
- Right sided graft failure is a major complication in this population
- Short term mortality is significantly higher than in heart transplantation following acquired heart disease or other types of congenital defects.

Prognosis: Unmet medical needs(cont.)

As patients reach adolescence, cardiovascular function begins to deteriorate as manifested by:

- Decreasing aerobic exercise tolerance.
- Signs and symptoms of right sided heart failure including ascites and peripheral edema

Life threatening complications become increasingly common in the late teens and early twenties:

- Protein losing enteropathy
- Plastic bronchitis
- Hepatic cirrhosis
- Overt heart failure resulting in death or transplantation

Prognosis: Unmet medical needs(cont.)

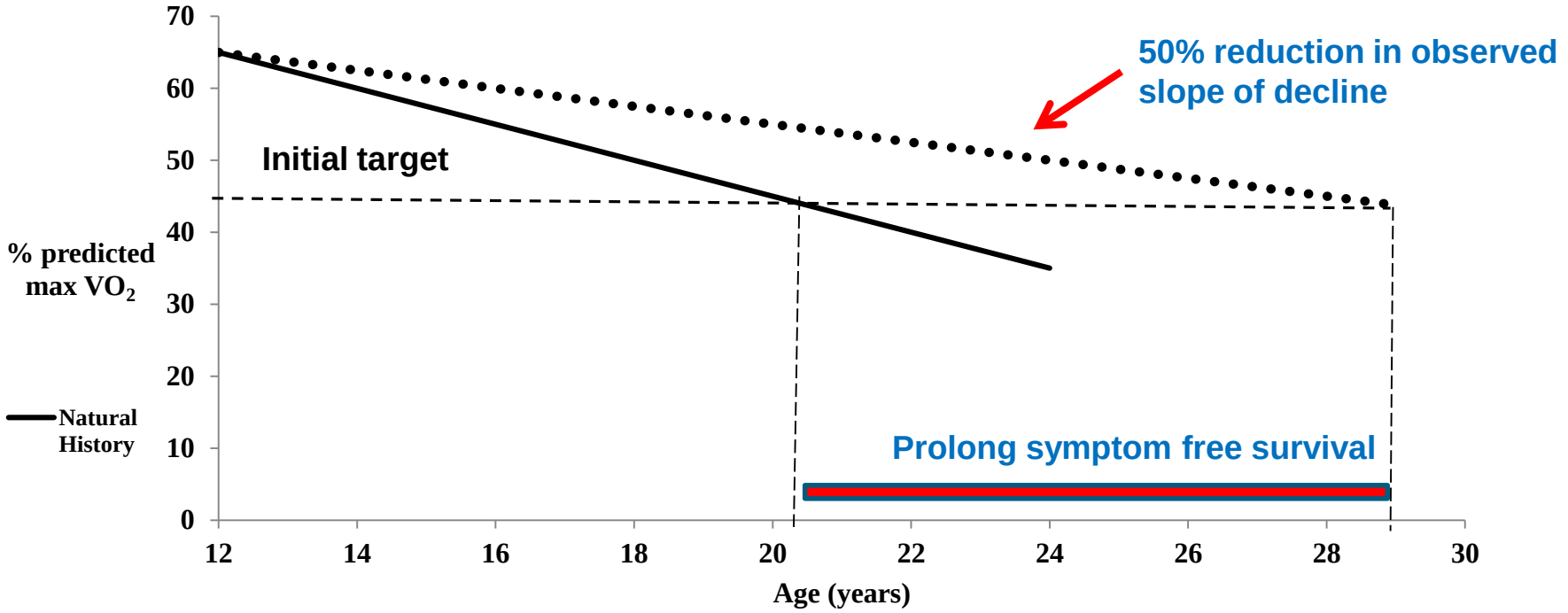


Figure. Projected decline in percent predicted max. VO_2 vs. age in years. Comparison of baseline projected rate of decline in percent predicted max. VO_2 (solid line) compared to a 50% reduction in the slope (dotted line). Note that there is an approximately 8 year difference between the two conditions for reaching 45% of predicted max. VO_2 (horizontal dotted line).

The projected rate of decline in aerobic capacity for the PHN Fontan Study Cohort.

The risk of serious complications will rise considerably once past the age of twenty.

Prognosis: Unmet medical needs(cont.)

Facts on Fontan Patients

- Limited ability to augment pulmonary blood flow due to a lack of a sub-pulmonary ventricle.
- Aerobic exercise capability decreases significantly during their adolescence
- The risk of hospitalization and Cardiac death rise significantly in the second and especially in the third decade of life.
- Non-cardiac complications such as protein losing enteropathy, plastic bronchitis and liver failure occur with increasing frequency beginning in the second decade of life.

No approved treatments are available at this point

- Ace inhibitors, beta blockers, aldosterone antagonists, inotropic drugs are used when there is systemic ventricular failure but are ineffective for failure of the Fontan circulation.
- There are no approved medications specifically indicated for the treatment of single ventricle heart disease.

Safety of Udenafil

35+ clinical trials have been performed with udenafil (3 studies done in Japan in addition)

More than 6,000 subjects were involved in the udenafil studies out of which 4,000+ have been dosed with udenafil

	Phase I Studies	Phase 2 Studies	Phase 3 Studies	Indication
US, EU, Korea	24	3	8	ED
Japan*	1	2	-	BPH

**In the Japanese studies, a total of 1,488 subjects were involved (out of which 923 subjects were introduced to Udenafil at least once)*

No Major safety issues were found during the studies other than the minor ones that were already known for PDE5 inhibitors in general

Fontan Udenafil Exercise Longitudinal Assessment (FUEL) – Ph 3 Pivotal Study

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- The FUEL trial is being run in conjunction with:
  - NHLBI (National Heart Lung and Blood Institute)
  - PHN (Pediatric Heart Network)*
- The FUEL trial is comprised of 30 sites, including US, Canada and South Korea

**PHN (Pediatric Heart Network): established in 2001 by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH). It was created to help doctors and nurses design and carry out clinical research so that children with heart disease can receive high-quality, evidence-based care.*

Pediatric Heart Network

NIH National Heart, Lung, and Blood Institute

Fontan Udenafil Exercise Longitudinal Assessment (FUEL) – Ph 3 Pivotal Study

- **Study Design (randomized, double-blind, placebo controlled)**

  - Total number of subjects : 400
  - Duration of Drug Administration : 6 months
  - Study Sites : 30 hospitals
  - Age : 12 to below 19 who have undergone Fontan surgery
  - Dosing : Udenafil (87.5mg) BID (twice a day for 6 months)

  ☞ **Completed randomization in June 2018!!**

- **Study Endpoints**

  1. Primary Outcome

     → Improvement in the aerobic capacity (Max VO_2)

  2. Secondary Outcome

     1) Improvement in the Myocardial Performance Index (MPI)

     2) Change in log-transformed Reactive Hyperemia Index derived from the EndoPAT device.

     3) Change in serum BNP level (Biomarker for heart failure)

※ Max VO_2: Maximum Oxygen Consumption, BNP : Brain-type natriuretic peptide

FUEL Open Label Extension (OLE) Study

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- **Study Design (Open-label)**

  - Total number of subjects : 300
  - Duration of Drug Administration : 24 months (recently increased from 12 months)
  - Study Sites : Same as FUEL
  - Age : Same as FUEL
  - Dosing : Same as FUEL

- **Study Endpoints**

  1. Primary Outcome
     → Long term Safety
  2. Secondary Outcome
     1) Improvement in the aerobic capacity (Max VO_2)
     2) Improvement in the Myocardial Performance Index (MPI)
     3) Change in functional health status measured by the full scale Peds QL
     4) Change in serum BNP level (biomarker for heart failure)

Fontan-associated Liver Disease (FALD) Study

- **Study Design**

  - Total number of subjects : 100 (from OLE Study)
  - Dosing : MZ101 BID

- **Study Endpoints**

  1. Primary Outcome

     → Liver stiffness as measured by Shear Wave Ultrasound Elastography or Magnetic Resonance Ultrasound

  2. Secondary Outcome

     1) Effect of drug therapy on BNP
     2) Effect of drug therapy on N-terminal BNP (NT-proBNP)
     3) Effect of drug therapy on MicroRNA measures
     4) Effect of drug therapy on Enhanced Liver Fibrosis (ELF)

※BNP : Brain-type natriuretic peptide, MicroRNA : Ribo-Nucleic Acid, ELF : Enhanced Liver Fibrosis

Early Access Program (EAP)

- ***What is EAP?***

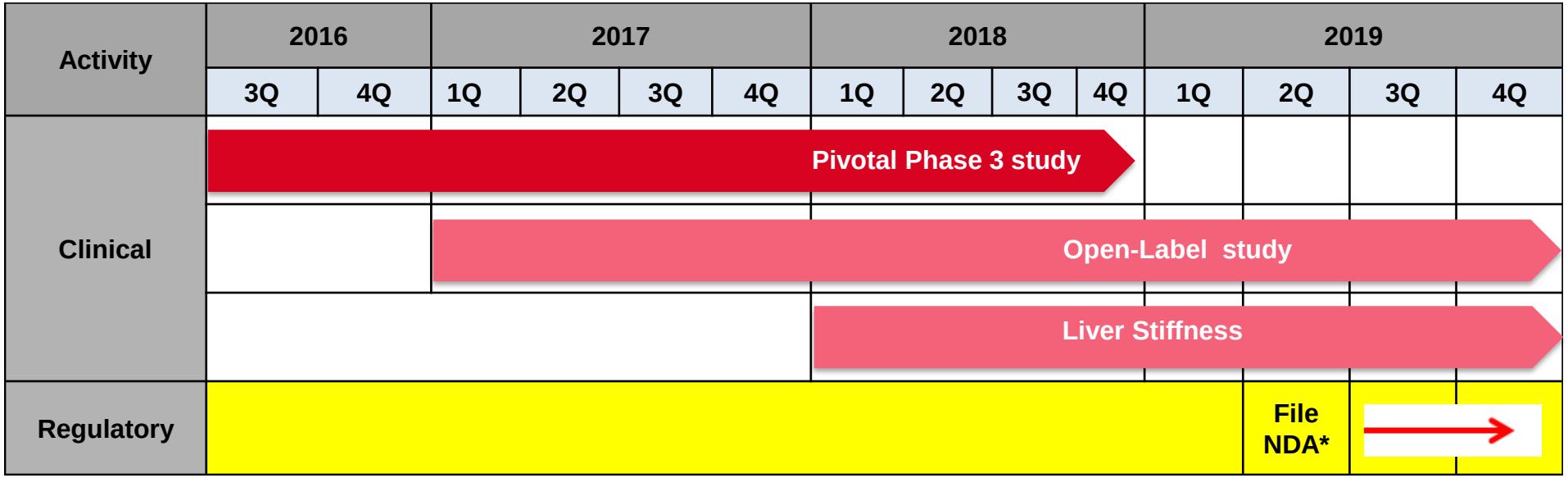
  - EAPs offer ethical, compliant, and controlled mechanisms of access to investigational drugs outside of the clinical trial space and before NDA approval and commercial launch of the drug to patients with life-threatening diseases having no treatment options available.

- **Benefits?**
  - Compassionate use by making drug available during NDA pendency
  - Immediate market access of drug upon FDA approval
  - Development of positive relationships with key opinion leaders (KOL) during NDA pendency
  - Data captured from the implementation of EAP supports global commercialization strategies

- **Mezzion is in the process of implementing an EAP for the Fontan patients**

Development Timeline for Fontan

- **Product Development Timeline**



*** Accelerated review (in 6 months) to be requested**

Market Opportunity

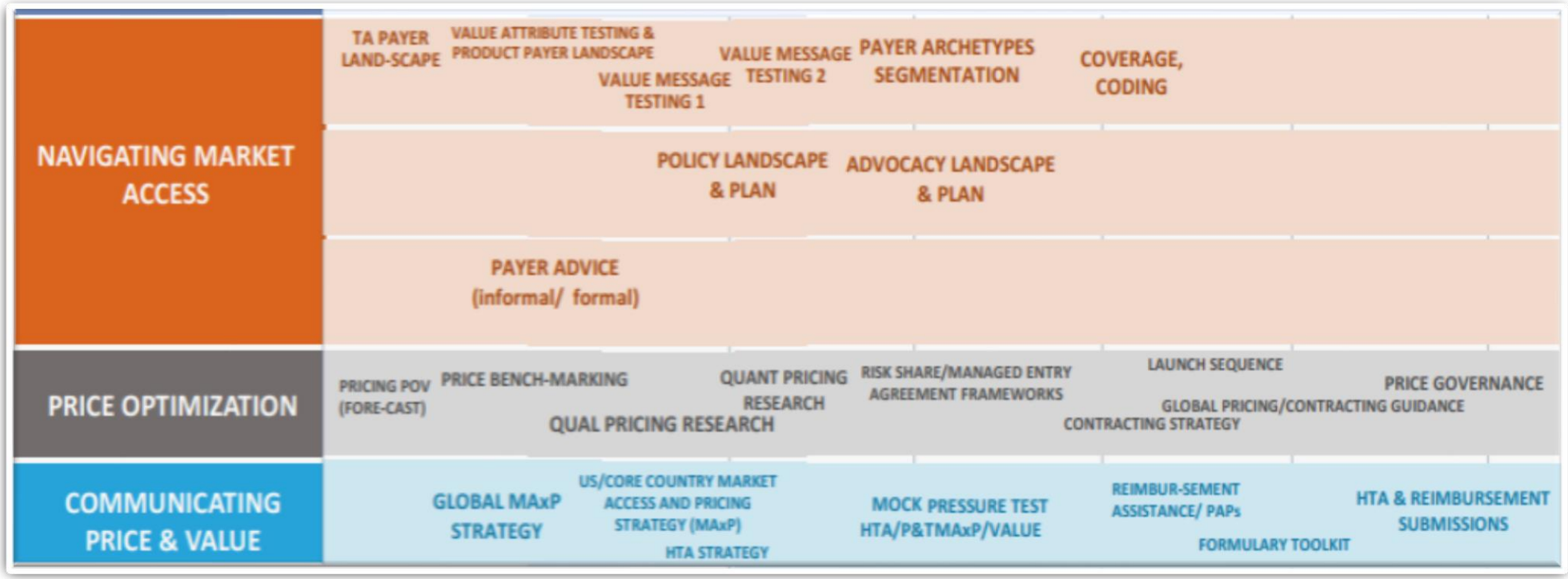
- **Udenafil Future Positioning & Exclusivity**
  - Outstanding safety record – based on chronic daily use experience in Korea, Turkey and Japan for ED and BPH

    ※ED : Erectile Dysfuntion, BPH : Benign Prostate Hyperplasia
  - Patents applied for globally covering method of use and oral compositions of matter (2035 expiration)
  - Patent Term Extension available in United States
  - Seven year orphan drug exclusivity in US
  - Five year NCE exclusivity in US
  - Three year data exclusivity in US
  - Pediatric Exclusivity possibly available in US
  - Readily reachable target audience – ideal for specialty detailing

- **In summary – Modest technical & commercial risk**

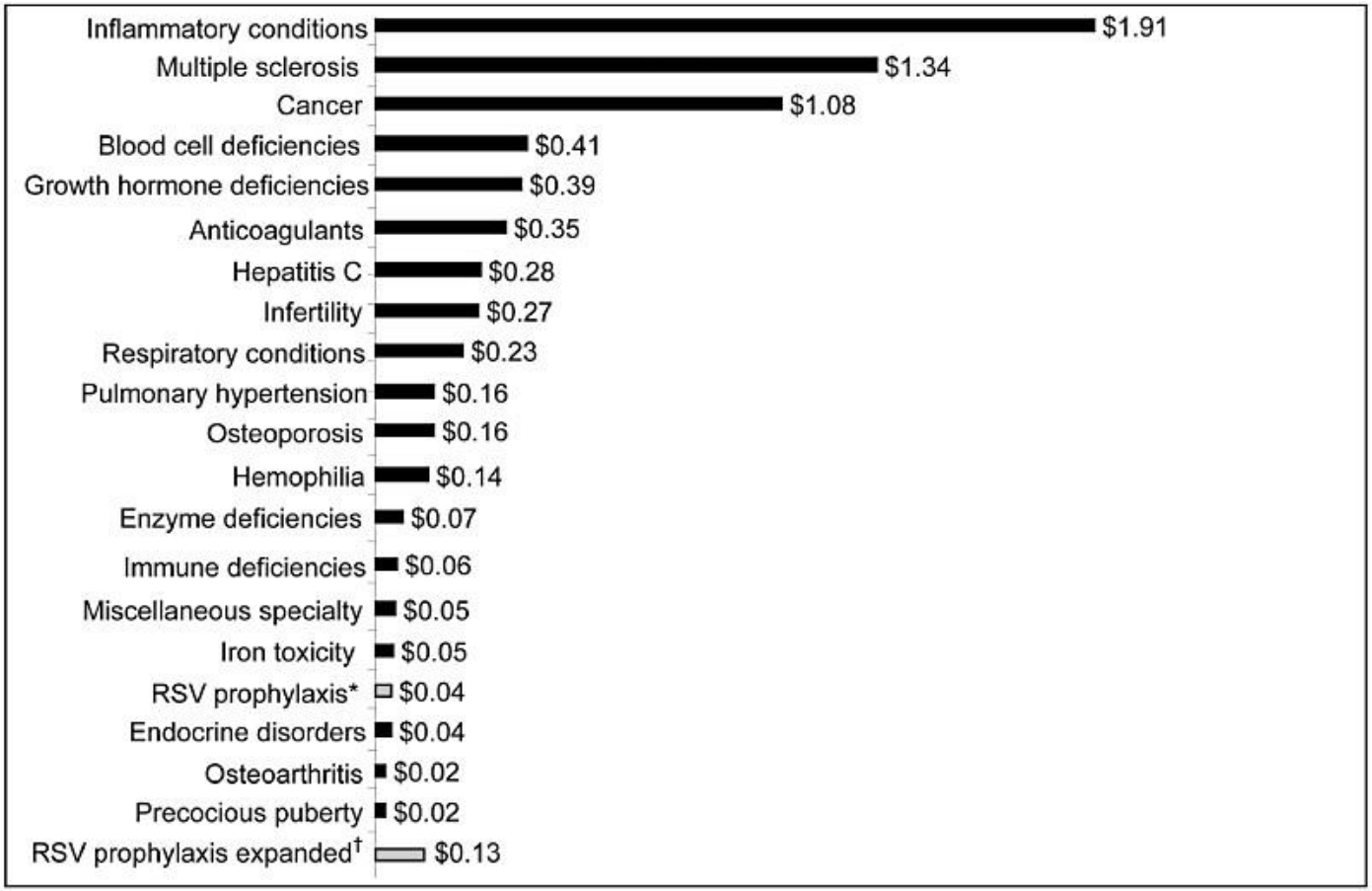
Payer Engagement Program for Mezzion

- **Mezzion engaged with leading rare disease pricing group to begin:**
  - Price validation
  - Value story required for pricing sensitivity
  - Pre-approval pricing to ensure large payer adoption at the time of NDA approval



PMPM (Per Member Per Month)

- **One of the major tasks in the current US public healthcare system**
- **Cost per patient for a month is calculated which is used to decide on the drug price by the payer**



*** Volume 13, Number 1 Value in Health (2010)**

Orphan and Rare Disease Pricing

We expect favorable pricing commensurate with the pricing for other orphan drug products with similar patient populations.

Non-US Market (EU)

- **Opportunities in EU**

  - MA through EMA by CP(centralized procedure) is possible which can allow the registration in 28 EU member countries at the same time.
  - An access to the population of more than 500 million (including UK) with the guaranteed market exclusivity of 12 years (10 years for the orphan status and +2 years for being a pediatric drug) when approved.
  - Considering the ability to afford the medication compared to the reimbursement rate and its population, the potential size of the market will likely be around 1/3 of US.
  - Market Approval is possible without additional clinical trials, which enables the market entry after the approval in US.

Epidemiology in Japan

According to the Japanese Registry of all Cardiac and Vascular Diseases, the Fontan operation population was 357 in 2015. Approximately 20 years after Fontan surgery, SVHD are recognized in 50% of patients.

There are over 3,000 SVHD patients in Japan currently and SVHD patients will be increased to 5,000 in the next 10 years (Japanese Intractable Diseases Information Center).

In other words, we may be looking at the 10,000 post Fontan surgery patients about 50% of them to be subject to the post Fontan syndrome treatment in 10 years of time.

Japan Market

- **There are about 3,000 SVHD patients currently which will be increased to 5,000 in next 10 years**
- **At Tokyo Women 's Medical University, there are about 700 patients in total**
  - The target patient number for Udenafil treatment is 500 to 1000 in Japan, but it will be increased because the after Fontan operation patients will increase the number and the patients will grow to adult.
  - This number only counts for the patients between the age of 12 to 18 which is the inclusion criteria of the current phase 3 study (FUEL).
- **In Japan, the drug price for orphan drugs is relatively high and comparable to that of the originated country**
- **In Japan, we are planning to file an application for the Orphan drug designation which will give us a market exclusivity of 10 years.**

Development Plan in Japan

- **Current Status in Japan**

  - Probing to enter into the market without any human clinical trials (ie. submit JNDA with the top-line data from the FUEL study)

  - Planned to have a pre-consultation meeting with PMDA to find out the possibility with no additional clinical trials in Japan

- **Udenafil in Japan**

  - According to a PK study result, no significant difference found between the Japanese and the non-Japanese for udenafil

Thank you