Patient-centric designs in orphan diseases: Case Study #1

Development of Compound A for Adolescent Schizophrenia 13-17 Years Old with a Global Pediatric Development Program for US and EU

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Adolescent Schizophrenia

- A serious mental illness
- Cause is unknown, hypothesized the combination of brain changes, biochemical causes, genetic and environmental factors
- Early diagnosis and treatment are important
- Schizophrenia is in 2/3 of the cases a life-long disease that can be controlled but not cured
- Prevalence in adolescent population ~0.5%
- There is significant unmet medical need for new treatments
- Pharmaceutical companies are mandated to develop treatments for adolescents if they want to develop it for adult population
- Placebo-controlled clinical trials are burden to patients, thus the number of patients tested need to be minimized for ethical reasons

Development of Compound A for Adolescent Schizophrenia 13-17 Years Old with a Global Pediatric Development Program for US and EU

- Compound A got developed for adult schizophrenia for US and EU and pediatric plans were submitted at the required timeframes for US (2013) and EU (2012) with the pediatric plans
- A global study with multiple countries and sites got initiated in 2017
- After 3 years of enrollment the number of randomized patients is below 150
- Rare occurrence in adolescents first episode patients require separate studies, placebo use is challenging for clinical studies (risk of country regulatory authority and central ethic's committee rejections)

A Global Pediatric Program, the Beginning

	US Program	EU Program
Reg. Status	**PSP approved (2013)** PAC (2015) PPSR (2018)	**PIP approved (2012)**
Patient population	**Waiver 0-12 years old**	
	Studies 13-17 years old	
Study 1/ PK	**Phase 1 MAD** to characterize adolescent PK and support Phase 3 dosing	

Study 2 / Efficacy	N~400 approved in US
	• ***Short-term phase***
	  • 6 weeks , IP vs. placebo vs active reference,
		N~ 500 approved in EU
		• ***Short-term phase***
		  • 6 weeks , IP vs. placebo vs. active reference,
		• ***Maintenance Phase***
		  • 26 weeks, IP vs active comparator blinded maintenance of effect

Study 3/ Long – term safety exposure	**Study 3**: 24 months-OL study, roll over patients from Study 2 Minimum exposure: 100 patients at 6 months and need 12 months exposure Agreement for filing is the above minimum 12 months exposure	**Study 3**: 1 year-OL study, roll over patients from Study 2. Minimum exposure: ≥ 100 patients enrolled for 24 months, min 25% from EU

2017 An Opening in EU About Maintenance of Effect Studies

	US Program	EU Program

Study 2 / Efficacy	N~400 approved in US
	• ***Short-term phase***
	  • 6 weeks , vs. placebo vs. active reference,
		N~ 500 approved in EU
		• ***Short-term phase***
		  • 6 weeks , IP vs. placebo vs. active reference,
		• ***Maintenance Phase***
		  • 26 weeks, IP vs. active comparator blinded maintenance of effect
		• **Extrapolation study for the maintenance of effect**

Study 3/ Long –term safety exposure	**Study 3**: 24 months-OL study, roll over patients from Study 2 Minimum exposure: 100 patients at 12 months Agreement for filling is the above minimum 12 months exposure	**Study 3**: 1 year-OL study, roll over patients from Study 2. Minimum exposure: ≥ 100 patients enrolled for 24 months, min 25% from EU

An RfM got submitted to PDCO to modify the PIP and substitute the relapse prevention phase of Study 2 with an extrapolation study for the maintenance of effect

2020 New FDA Guidance on PK Extrapolation for Adolescent Schizophrenia

	US Program	EU Program

Study 2 / Efficacy	N~400 approved in US
	• ***Short-term phase***
	  • 6 weeks , IP vs placebo, active reference,
	• **Similarity of PK exposure between adult and adolescents is the basis of extrapolation of short-term efficacy data for adolescents**
		N~ 500 approved in EU
		• ***Short-term phase***
		  • 6 weeks , IP vs placebo vs. active reference,
		• ***Maintenance Phase***
		  • 26 weeks, IP vs. active comparator blinded maintenance of effect
		• **Extrapolation study**

Study 3/ Long –term safety exposure	**Study 3**: 24 months-OL study, roll over patients from Study 2 Minimum exposure: 100 patients at 12 months Agreement for filling is the above minimum 12 months exposure	**Study 3**: 1 year-OL study, roll over patients from Study 2 Minimum exposure: ≥ 100 patients enrolled for 24 months, min 25% from EU

2020 Submission of RfM to PIP to Eliminate Short Term Efficacy Study TBD

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		• ***Maintenance Phase***
		  • 26 weeks, IP. vs active comparator blinded maintenance of effect
		• **Extrapolation study**

Study 3/ Long –term safety exposure	**Study 3**: 24 months-OL study, roll over patients from Study 2. Minimum exposure: 100 patients at 12 months Agreement for filling is the above minimum 12 months exposure.	**Study 3**: 1 year-OL study, roll over patients from Study 2. Minimum exposure: ≥ 100 patients enrolled for 24 months, min 25% from EU

- High risk of rejection
- Back-up plan: New RfM to reduce sample size to comparable studies and US approved sample size (N~400)