W1042

Enabling Clinical Assessment of Maralixibat for Rare Pediatric Liver Disease via Real Time Adaptive GMP Manufacturing

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PURPOSE

Increasing diversification within clinical research to develop treatments for orphan, rare and pediatric disease is challenging the ability of conventional drug product supply chains to support pivotal Phase II/III patient trials.

Traditionally a limited number of fixed product variants are manufactured at large scale with a defined shelf-life to cover a predicted recruitment period and the dosing of several hundred or thousand subjects. However, this approach is inefficient when the study population is small and a highly interactive relationship between subject and product is needed. Formulations need greater levels of personalization (for example with mg/kg or mg/m^2 dose algorithms), whilst protracted and unpredictable recruitment rates place a high demand on ensuring availability of the right drug product in the right location at the right time.

Maralixibat (SHP625; formerly LUM001) is currently under development across several global clinical trials for the treatment of rare pediatric liver diseases, Alagille Syndrome, an autosomal genetic disease, and Progressive Familial Intrahepatic Cholestasis, a group of cholestatic conditions. A high level of customization of the drug product is required in these studies based upon the treatment needs of the protocol. Here we describe how an innovative real time adaptive Good Manufacturing Practice (GMP) manufacturing and supply platform has been able to support studies on a global basis.

METHOD(S)

A fixed volume, variable concentration solution formulation of maralixibat was developed for the target pediatric patient population. Drug product requirements had to be customized to meet the following individual patient and study needs:

- mg/kg dosing across a 5 - 70kg body weight range
- Dose escalation phase to one of four treatment regimens followed by a treatment phase
- Adjustment of dose if body weight varied by more than ±10% during treatment
- Allowance for dose titration based on tolerance
- Randomized and blinded study design
- Unpredictable recruitment rates across multiple sites and countries

A novel GMP manufacturing and supply model was established to ensure the availability of personalized drug products as quickly as possible after an eligible subject was identified or a product resupply was required (Figure 1).

- Drug products requested by investigator via an electronic form or an interactive web response system (IWRS)
- Bespoke drug products manufactured, labelled and released within 2 days with full Quality Assurance (QA) and Qualified Person (QP) oversight at Quotient Sciences (UK) (Figure 2)
- Patient packs dispatched immediately via courier to the clinical site

One bottle of maralixibat solution contained sufficient product for 3 weeks treatment. Four bottles of the drug product was typically supplied in each packaging configuration (Figure 3) for each patient (i.e. 12 weeks medication in total).

RESULT(S)

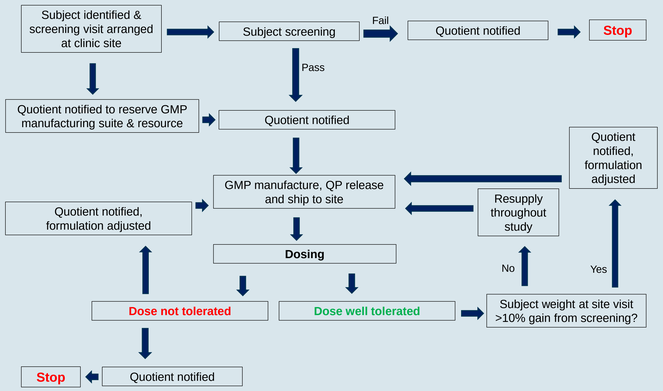

Figure 1: Real-time adaptive GMP manufacturing and supply for Maralixibat pediatric clinical programs

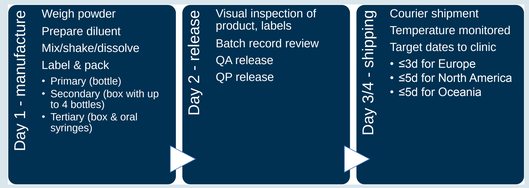

Figure 2: 48h manufacture and release cycle for Maralixibat solution

Figure 3: Primary, secondary and tertiary packaging configurations for Maralixibat solution

Maralixibat drug product supply needs for 6 separate clinical studies have consistently been met. To date over 1300 personalized formulations have been manufactured under GMP and supplied for dosing to pediatric patients on a global basis. Drug products have been successfully delivered to 180 patients at over 25 clinical sites in 8 countries.

Most drug products have been despatched to North America during the course of the clinical studies (48%), closely followed by Europe (43%), with 9% going to Oceania (Figure 4). Target shipment times were set as ≤3 days (for Europe) and ≤5 days (for US and Oceania).

RESULTS(S)

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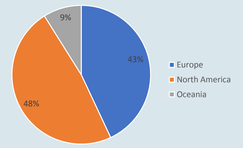

Figure 4: Breakdown of geographical regions for product supply

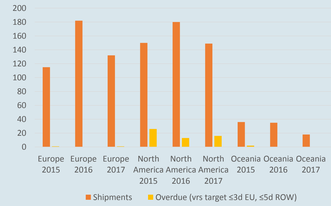

Figure 5: Product supply timelines by region

An assessment of data from January 2015 to August 2017 has confirmed that over 94% of deliveries were achieved within the very tight delivery times, with most of the outliers observed for drug product shipped to North America due to slight FDA import delays (Figure 5). Excursions have been minor in nature however with over 99.7% of deliveries arriving within 10 days from dispatch.

CONCLUSION(S)

A flexible, real-time adaptive GMP manufacturing model is required to support the increasing requirement for clinical trial conduct in small patient populations with challenging trial designs and treatment algorithms. To enable Phase II trials of maralixibat in rare pediatric liver disease, an innovative platform was created allowing real time adaptive GMP manufacturing and supply of personalized drug products on a global basis within 1-3 weeks of notification.

This model has been proven to support a wide variety of oral drug products, regardless of the manufacturing technology required (Table 1). Formulations can be designed based on physicochemical and biopharmaceutic needs of the drug molecule and be manufactured and supplied rapidly and flexibly for patient-based trials.

Product Type	Manufacture	QC testing	QA/QP release	Total # days
API in Bottle / Capsule	1	2	1	**4**
Solution / Suspension	1	2	1	**4**
Formulated API in Bottle / Capsule	2	2	1	**5**
Solubilised API in bottle or Capsule	3	2	1	**6**
Tablet (Immediate Release)	3	3	1	**7**
Tablet (Spray Dried Dispersion)	4	3	1	**8**
Tablet (Modified Release)	3	4	1	**8**

Table 1: GMP manufacturing and release cycle times for various drug product formulations

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