A case study of a successful RTOR submission and approval for Rylaze

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ABSTRACT

The RTOR (Real-Time Oncology Review) program, launched by the FDA's Oncology Center of Excellence and Office of Oncologic Diseases in February 2018, aims to expedite the review process for oncology treatments by allowing for early submission of top-line efficacy and safety data. This enables FDA reviewers to begin the review process sooner and brings treatments to patients more quickly. The program also improves the review quality and early engagement between the sponsor and FDA. This paper examines the experience of the Programming team at Jazz Pharmaceuticals, which successfully submitted and gained approval for Rylaze/JZP458 (BLA, June 2021 and sBLA in Nov 2022), a part of chemotherapeutic regimen for acute lymphoblastic leukemia and lymphoblastic lymphoma under the RTOR program. It covers the team's role, involvement, and approach in the submission process, including steps taken to address post-submission requests from the FDA, providing valuable insights for anyone looking to use the RTOR program in the future.

INTRODUCTION

This paper examines the experience of the programming team at Jazz Pharmaceuticals, who contributed towards the preparation of an RTOR submission for Rylaze/JZP458 and set a record for the most expeditious review and approval, for an original application for a New Molecule Entity through RTOR program. This paper will discuss the RTOR submission components required from Programming team and preparation efforts from the team.

RTOR SUBMISSION COMPONENTS AND TIMELINES

As per the FDA's RTOR guidelines, for any application to be considered for the RTOR program, the submission should demonstrate–

- Drugs likely to demonstrate substantial improvements over available therapy or meeting criteria for Expedited Programs.

- Straightforward study designs.

- Endpoints that can be easily interpreted (e.g., overall survival, response rates, etc.).

Figure 1 below provides an overview of the Rylaze/JZP458 study design.

Jazz Pharmaceuticals' cross-functional team grew more confident about Rylaze/JZP458's suitability to be considered under RTOR program after examining the FDA's guidelines and data. Consequently, they decided to seek the FDA's review process for Rylaze/JZP458 under the RTOR program. Subsequently, the Programming team reviewed the RTOR guidelines and timelines (as shown in Figure 2) to determine their responsibilities and develop an appropriate approach. According to the RTOR guidelines, the following components are necessary for 'Pre-submission.'

COMPLETE SDTM DATASET PACKAGE
Like any SDTM package submitted to FDA, the package submitted under RTOR program contains SDTM datasets in SAS® transport files (.xpt) format, data definition file (define.xml and related stylesheet), Annotated Blank CRF (acrf.pdf) and Clinical Study Data Reviewer's Guide (csdrg.pdf).

ADAM DATASET PACKAGE FOR KEY EFFICACY AND SAFETY TABLES/FIGURES
Like any ADaM package submitted to FDA, the package submitted under RTOR program contains ADaM datasets in SAS® transport files (.xpt) format, data definition file (define.xml and related stylesheet), Analysis Data Reviewer's Guide (adrg.pdf).

TOPLINE EFFICACY/SAFETY TABLES/FIGURES

Key efficacy and safety outputs are part of 'pre-submission' section as per guidelines, that includes supporting RTF and PDF files from Programming team.

SAS® PROGRAMS

Clean SAS Programs for ADaM datasets and Topline results in executable TXT format.

Study Design: Open-label, multicenter, dose confirmation, and PK study of Rylaze in patients (of any age) with ALL/LBL who are hypersensitive to *E. coli*-derived Asparaginases
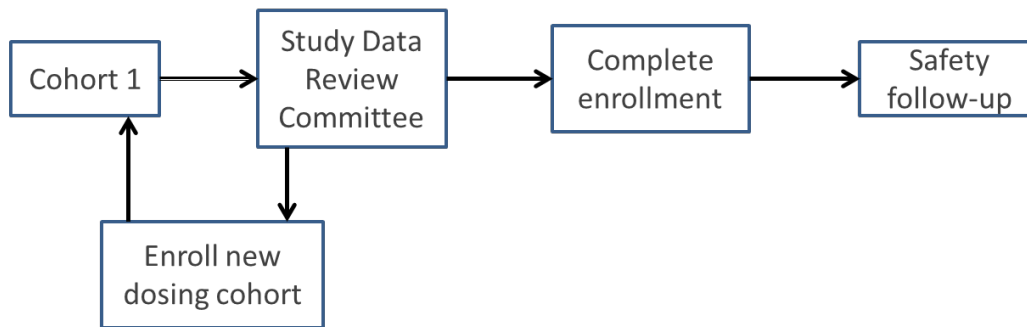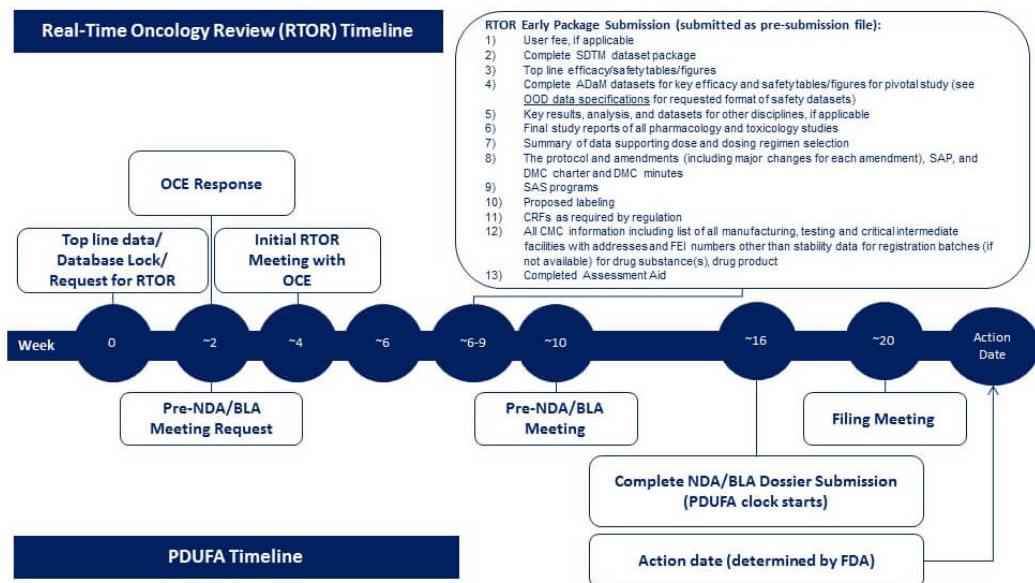

Figure 1. Overview of the Rylaze/JZP458 study design (ClinicalTrials.gov Identifier: NCT04145531)

Figure 2. General Real-Time Oncology Review (RTOR) Timeline

PROGRAMMING TEAM'S APPROACH TO PREPARATION

The internal timelines were being prepared by a cross-functional working group at Jazz Pharmaceuticals, which was a challenging schedule of three weeks to complete the entire package, including SDTM

Package, ADaM Package, Programs, and Outputs, starting from data extraction. However, as the submission deadlines drew near, the Programming team was able to reduce the timelines to two weeks. The fact that the study was an open-label parallel study proved to be helpful. The upcoming sections will elaborate on the proactive approach adopted by the team and how they succeeded in preparing for it.

COMMUNICATION

The key to a successful and fast-paced submission program is effective communication. All cross-functional teams must be aligned and working towards the same goal. The programming team collaborated with other teams to optimize the process and ensure high-quality submission packages. For instance, they worked closely with the Data Management team to ensure smooth data transfer and conducted programmatic quality checks to ensure the data received was acceptable. These checks included both known data issues and defensive programming blocks to verify expected versus actual data from CRF. The programming team also maintained open communication with the Biostatistics team to execute the output review plan and coordinated with the Regulatory Operations team to plan the data package transfer and upload it to the FDA's portal in the required eCTD format (M5 folder structure). In addition, the programming team collaborated with the Clinical Development and Label teams to provide the necessary information for inclusion in the submission package.

Effective communication was also essential for informing the study team of management's intention to approach the FDA for RTOR and planning the programming strategy at least six months in advance of the submission. This strategy involved keeping Programming and Biostatistics work in-house to maintain the required pace. The team also discussed providing the PopPK modelling team with data in SDTM format instead of Excel, as previously discussed, to reduce redundancy in work and increase confidence in the quality of source data for the PopPK modelling analysis

PROACTIVE PREPARATION FOR PROGRAMMING

The team took a proactive approach and worked on various internal initiatives to create a comprehensive package that meets the high standards required to succeed in all areas of communication discussed in the previous section.

INVOLVEMENT AS EARLY AS POSSIBLE

During the CRF and Electronic Data Capture System design phase of the study, the programming team took a proactive role in analyzing the data collection process while keeping in mind the CDISC standard mapping. This approach helped to streamline the process in advance.

PROGRAMMATIC RAW DATA CHECKS

To proactively detect any unintentional data points or missing data in the raw data, a defensive program was developed. Based on the findings from previous data transfers, the program was updated to run these checks for any future transfers. This approach allowed for the rapid identification of any data issues within the first hour or two of the data transfer, which increased confidence in the data quality and provided an additional cushion, avoiding the need to identify these issues much later during P21 checks or output reviews.

MULTIPLE INTERNAL RERUNS INCLUDING P21 CHECKS

The study design provided the team with the opportunity to conduct multiple internal reruns at various planned data extractions. These reruns involved programming raw data checks and refining programs to make them more dynamic and accommodate various data points. P21 checks were performed at all internal reruns of SDTM, ADaM, and Define.xml, providing additional confidence in the CDISC compliance of the data packages and avoiding any last-minute surprises. The team treated these reruns as actual runs, following the same timelines and review cycle as for the actual run. This approach helped the team become accustomed to the pace of the reruns and flexible enough to adjust accordingly for any unexpected issues.

EFFECTIVE USE OF EXISTING INTERNAL INFRASTRUCTURE

The team diligently reviewed the Statistical Analysis Plan (SAP) and Output Shells, ensuring that the output formats were compatible with Jazz Programming Standards and available Utilities/Macros. This approach helped to achieve consistent and accurate output generation repeatedly, increasing confidence and shortening the timelines as the actual submission milestones approached.

EFFECTIVE DRY RUN

During the first and/or only Dry run, the team solicited feedback from cross-functional teams, including Biostatistics, Clinical Development, PK, and Medical Writers. The team established clear expectations to receive feedback from these teams, then held a rigorous comments adjudication meeting to accommodate all changes as discussed.

DEDICATED CORE TEAM AND KNOWLEDGE TRANSFER PLAN

To successfully accomplish a goal, it is imperative to establish a committed core team. This minimizes the possibility of communication breakdowns and fosters a cohesive team dynamic. However, in reality, it can be challenging to ensure that the same dedicated team is available throughout the entire project duration. Nonetheless, a contingency plan via a knowledge transfer strategy was developed to mitigate any issues that might arise due to personnel changes. As a result, the likelihood of communication gaps was substantially reduced.

CHALLENGES AND LESSONS

COVID-19 PANDEMIC

While preparing for the submission of Rylaze/JZP458, the world was grappling with a pandemic. The cross-functional teams, like the rest of the world, were subject to lockdowns and almost everyone had to work remotely, with the exception of clinical sites and manufacturing. It was difficult to maintain team motivation and productivity in this situation. The team faced sporadic issues related to resourcing, but their commitment to prioritizing patients and ensuring that an important therapy was made available to them kept them going. Despite the challenges, team members were willing to step in for one another and fill in the gaps in case someone had to be absent due to pandemic-related reasons.

DATA ISSUES

Fresh data entry challenges surfaced, requiring the development of new programming checks that were then shared with the Data Management team to facilitate resolution and reconciliation. These new programmatic checks were subsequently added to the existing roster of programming checks for future Data extracts, which supported our objective of conducting productive data review meetings. Furthermore, the programming team's proactive approach of running programmatic data checks on the raw data and generating P21 reports after each internal rerun was instrumental in identifying these issues prior to the actual rerun, thereby avoiding any delays or the likelihood of inaccurate data.

PACE

As mentioned in the introduction section of the RTOR, we have observed how rapidly RTOR preparation can progress. However, proactive preparation facilitated the achievement of dependable and high-quality outputs. Multiple internal reruns were conducted, enabling the team to acquire the necessary momentum. Consequently, the team managed to create a submission package within two weeks from the Data extraction deadline, which included a validated and reviewed SDTM Package (comprising xpt, define.xml, and csdrg.pdf, P21 checks), ADaM Package (comprising xpt, define.xml, and adrg.pdf, P21 checks), as well as all supporting outputs for Clinical Study Report (CSR).

MULTIPLE PARALLEL DELIVERIES

During the RTOR preparation, there was an additional challenge due to the study design of Rylaze/JZP458 that required regular deliveries for the Study Data Review Committee (SDRC) meetings. The SDRC reviewed the efficacy and safety data and recommended a dosage determination. On certain

occasions, several preparations for upcoming deliverables were happening in parallel, requiring the team's flexibility in rapidly switching between planned deliverables. The efficient utilization of the Statistical Computational Environment within the department enabled the management and planning of multiple deliverables simultaneously, without affecting the timelines.

DATA UPLOAD TO FDA'S PORTAL

As a component of the RTOR submission preparation, the team was required to upload the cumulative data multiple times at the FDA's portal, commencing with BLA, and subsequently for sBLA, as outlined in the FDA's eCTD guidelines. The programming team collaborated with the Regulatory Operations team and ensured that the data transfers were monitored closely. To avoid confusing the reviewers and prevent unwarranted Information Requests (IR), the latest upload was tagged as "Replace" for subsequent transfers, rather than "New".

FDA INFORMATION REQUESTS

Following package submission, the team received few Information Requests (IRs) from the FDA. Given the fast-paced RTOR process, most of these IRs had short timelines (48 hours). As an example, one IR required generation of Adverse Drug Reactions (ADR) as per FDA's grouping suggestion and Lab Shift tables, with only 4 business days given to complete the task. After the cross-functional team discussed and interpreted the IR, programming team had just 1 business day left to perform report creation and validation and send it for wider team review. The study team successfully resolved the issue within the given timeline, thanks to the effective communication within the core cross-functional team, the efficient utilization of the available programming infrastructure, and the proactive strategy in place to handle any such IRs from the FDA.

CONCLUSION

To conclude, RTOR allows for the submission of preliminary safety and efficacy data ahead of a complete application, facilitating an earlier start to the FDA's evaluation process while prioritizing patient safety. This paper emphasizes the vital role and responsibilities of the Programming team throughout the process, acknowledging the fast-paced nature of the undertaking. The Programming team, in conjunction with cross-functional teams, employs strategic measures to ensure successful RTOR submissions by emphasizing collaboration and communication within the core group. The team proactively prepares programming activities, beginning with participation in CRF and database design and utilizing available programming infrastructure to produce reliable and repeatable quality outputs, resulting in a high-quality RTOR submission package within the given condensed timeline.

REFERENCES

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ACKNOWLEDGMENTS

RECOMMENDED READING

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https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd

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