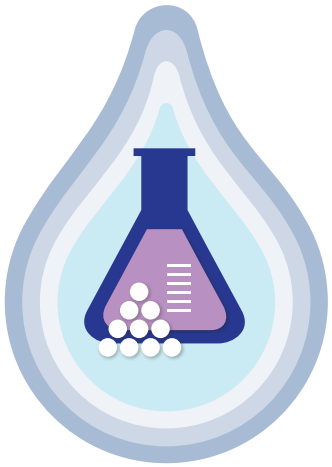
Catalent®



CASE STUDY

OptiForm® Solution Suite: Improved Bioavailability of Trio Medicines TML-2 in 12 weeks

Executive Summary

Trio Medicines Ltd (Trio) is a London-based pharmaceutical company, founded in 2005. Trio is developing treatments for unmet medical needs, including rare diseases, with the aim of improving the health and quality of life of patients worldwide. Trio's lead compound TML-2 is the acetyl prodrug of TML-1, a novel, well tolerated G-protein coupled receptor antagonist which shows clinical promise but has limited bioavailability owing to low solubility. The prodrug approach was only partially successful in increasing the solubility and bioavailability of TML-1, so Trio turned to Catalent for help. Utilizing OptiForm® Solution Suite platform, Catalent's experts screened 3 formulation technologies, and provided 4 formulation prototypes, in only 12 weeks. In 3 of the 4 prototypes, bioavailability of TML-2 was enhanced substantially.

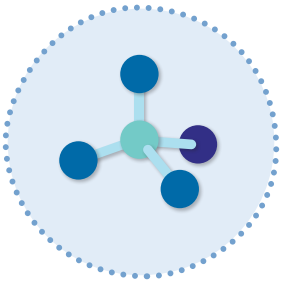
The Challenges

MOLECULE PROPERTIES	BCS class II molecule • Poor aqueous solubility • High permeability but possible strong efflux
TARGETED BIOAVAILABILITY	3-5x higher
CHALLENGES	Limited molecule characterization Molecule already in clinic - needed fast turnaround for alternatives Small company with limited budget Prodrug approach had failed to increase bioavailability to the desired level for clinical studies

The Catalent Solution

Catalent's Science & Technology advisors utilized Optiform® Solution Suite, an integrated platform with a structured 3-step approach: **ASSESS, ENHANCE & DELIVER**.

DEVELOPMENT DELIVERY SUPPLY

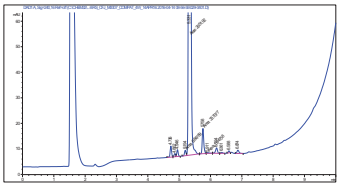


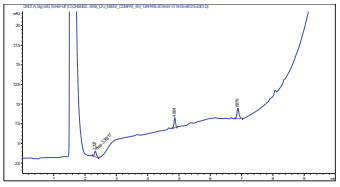
ASSESS Thoroughly assess the molecule's physical and chemical properties. Catalent conducted a series of assessments of the molecule's physicochemical properties.

1 CHEMICAL COMPATIBILITY

HPLC analysis of samples stored at high temperature to monitor growth of degradation products. In some excipients, the product showed accelerated degradation highlighted in red in the table below.

Excipient	Chemical Description	Main Peak % Area	Impurities Total % Area
Initial (TML-2)		99.96	0.62
Excipient 1	Triglyceride	99.31	0.69
Excipient 2	Lipophilic surfactant	97.18	2.82
Excipient 3	Triglyceride	99.19	0.81
Excipient 4	Hydrophilic cosolvent	97.36	2.64
Excipient 5	Fatty acid	97.78	2.22
Excipient 6	Glyceride ester	98.48	1.52
Excipient 7	Polymer	99.13	0.87
Excipient 8	Polymer	99.16	0.84
Excipient 9	Polymer	98.76	1.24
Excipient 10	Polymer	99.16	0.84
Excipient 11	Polymer	99.19	0.81
Excipient 12	Lipophilic surfactant	97.14	2.86



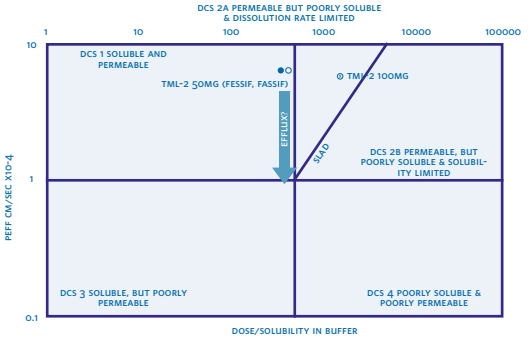


2 MOLECULE SOLUBILITY & DCS CLASSIFICATION

HPLC analysis of solubility in different buffers and biorelevant media. Recheck PXRD. Placement of molecule on DCS graph.

Media	Solubility (g/mL)	PXRD
BRB pH 1	>16000	No residual solids available
BRB pH 2	7293	Matches input material
BRB pH 4	412	Matches input material
BRB pH 6	114	Slight loss of crystallinity
BRB pH 8	102	Matches input material

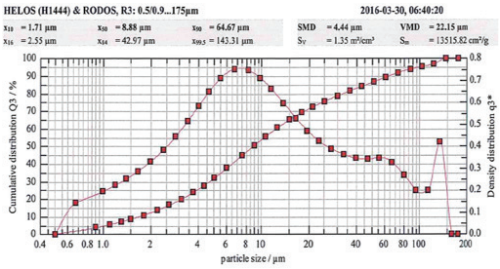
Buffer Condition	4 hours, g/mL	24 hours, g/mL	PXRD
BRB pH 1	8034	8421	Matches input material
BRB pH 2	114	116	Matches input material
BRB pH 4	145	148	Matches input material



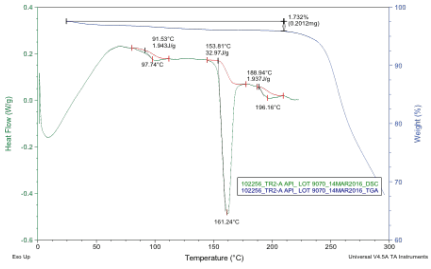
3 SOLID STATE CHARACTERIZATION

Analysis of Particle Size, DSC, Microscopy, DVS and PXRD

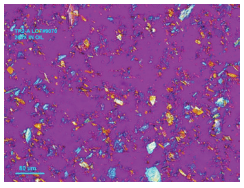
PARTICLE SIZE BY LASER DIFFRACTION



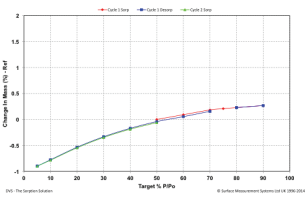
DIFFERENTIAL SCANNING CALORIMETRY WITH THERMOGRAVIMETRIC ANALYSIS



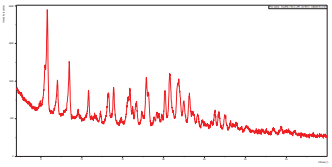
OPTICAL MICROSCOPY

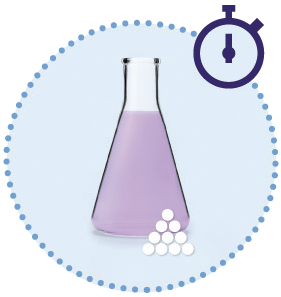


DYNAMIC VAPOR SORPTION



POWDER X-RAY DIFFRACTION

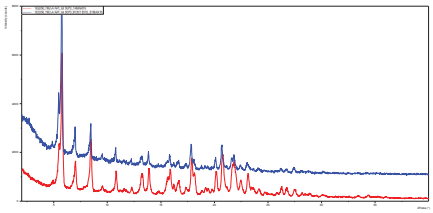




4 MOLECULE STABILITY

Analysis of PXRD at high RH, solid state and solution state stability (pH, light and peroxide)

PXRD AT HIGH %RH



SOLID STATE STABILITY / TEMPERATURE

Condition		Impurity (% Area) RRT 0.80	RRT 0.93	RRT 0.96	RRT 1.20	RRT 1.22	Total Related Impurities (% Area)
Initial		0.22	0.07	0.34	0.09	0.06	0.78
RT	Open	0.18	0.07	0.44	0.06	0.06	0.81
	Closed	0.24	0.06	0.39	0.06	0.05	0.80
40C	Open	0.20	0.06	0.48	0.06	0.05	0.85
	Closed	0.20	0.08	0.50	0.06	0.05	0.89

SOLID STATE STABILITY / LIGHT

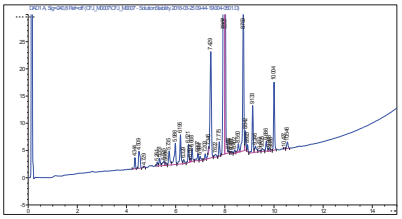
Condition	Impurity (% Area) RRT 0.27	RRT 0.65	RRT 0.80	RRT 0.93	RRT 0.95	RRT 1.11	RRT 1.19	RRT 1.21	RRT 1.22	RRT 1.33	RRT 1.44	RRT 1.45	RRT 1.57	RRT 1.85	Total Related Impurities (% Area)
Initial			0.22	0.07	0.34		0.09		0.06						0.78
1xICH Dark Control			0.23	0.07	0.41		0.09		0.06						0.86
1xICH	0.52	0.11	0.43	0.06	2.32	0.45	0.08	0.11	0.05	0.07	0.22	0.15	0.12	0.07	4.76

SOLUTION STATE STABILITY/MEDIA/TEMP/PEROXIDE/LIGHT

Buffer/Condition	Initial Main Peak Area (mAU*s)	Final Main Area (mAU*s)	% Degradation
pH 1.6 SGF/40C/24h	1525	1253	18
pH 6.5 FaSSIF/40C/24h	1510	1475	2
pH 6.5 FeSSIF/40C/24h	1483	1450	2
0.1% Peroxide at pH 6	1406	3	> 99
Light stability at pH 2, 1xICH	1494	18	> 98
Light stability at pH 6, 1xICH	1529	25	> 98

SOME ACID DEGRADATION OBSERVED AND SEVERE DEGRADATION IN PEROXIDE & LIGHT

EXAMPLE HPLC TRACE



The molecule was classified as a DCS IIa (limited by rate of dissolution, rather than absolute solubility) with some stability issues (not uncommon for a prodrug).

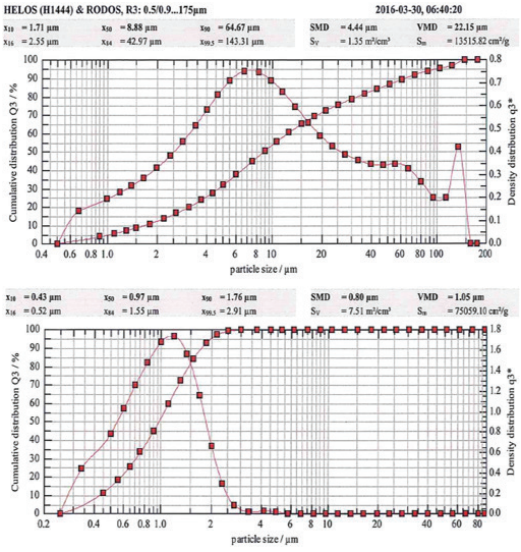
ENHANCE Evaluate multiple technologies in parallel. Based on the data from the ASSESS phase, Catalent's experts assessed the potential of 3 formulation technologies to enhance the molecule's bioavailability: lipid formulation (5), amorphous solid dispersion (6) and particle size engineering (7).

5 LIPID SOLUBILITY SCREEN

Vehicle	Incubation Temp, °C	HPLC Solubility (mg/g)	PXRD of Residue
Excipient 27	25	0.04	Pattern B
Excipient 28	25	0.06	Pattern B
Excipient 1	25	1.12	Pattern A
Excipient 3	25	0.35	Pattern A
Excipient 12	40	29.4	Pattern B
Excipient 5	25	3.41	Pattern A
Excipient 13	25	16.3	Pattern C
Excipient 14	25	22.3	Pattern B
Excipient 4	25	261	Pattern B
Excipient 6	25	189	Pattern B
Excipient 15	40	25.2	Pattern A
Excipient 16	25	84.1	Insufficient residual solid
Excipient 17	25	4.55	Pattern B
Excipient 18	25	0.31	Pattern D
Excipient 19	25	32.5	Pattern D
Excipient 20	25	1.67	Pattern A
Excipient 21	25	126	Pattern B
Excipient 22	25	3.49	Pattern B
Excipient 23	40	21.1	Pattern A
Excipient 24	25	40.3	Insufficient residual solid
Excipient 25	25	33.6	Pattern B
Excipient 26	25	40.0	Pattern B
Excipient 26	25	40.0	Pattern B

GOOD SOLUBILITY FAIR SOLUBILITY POOR SOLUBILITY

6 PARTICLE SIZE ENGINEERING

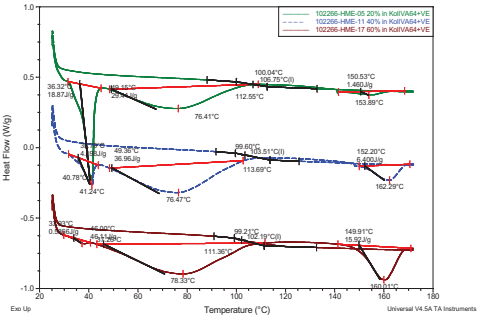


Particle Size Required = <83um (FaSSIF)

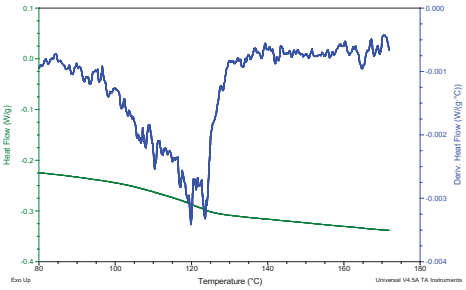
PARTICLE SIZE REDUCTION

7 AMORPHOUS SOLID DISPERSION

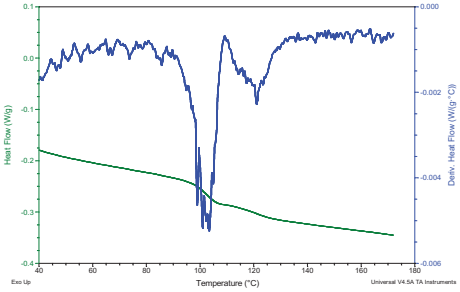
POLYMER MISCIBILITY (DSC)



EXAMPLE MISCIBLE



EXAMPLE NOT MISCIBLE



POLYMER MISCIBILITY SUMMARY TABLE

	Observations		
Polymer/Combinations	**20% API**	**40% API**	**60% API**
Excipient 11	Miscible	Immiscible	Immiscible
Excipient 7	Miscible	Immiscible	Immiscible
Excipient 8	Miscible	Immiscible	Immiscible
Excipients 11 & 7	Miscible	Immiscible	Immiscible
Excipients 11 & 30	Miscible	Immiscible	Immiscible
Excipients 11 & 31	Miscible	Immiscible	Immiscible

Results of technology screening:

- **Lipid Formulation:** TML-2 had good solubility in 4 excipients and fair solubility in another 7, providing sufficient options for development of a lipid formulation with 2.5-10% drug loading
- **Solid Dispersion:** Solid dispersion formulations were viable at a 20% drug loading
- **Particle Size Reduction:** TML-2 was micronized to the particle size target of D90<83µm (calculated from rearrangement of the dissolution equation)

DELIVER Provide prototypes for animal PK study, a full report with recommendations and all data, including 2 weeks' stability. Catalent provided 4 candidate formulations and a complete report to Trio within 12 weeks. Based on the assessment of physical/chemical properties, processability and fit to DCS classification, the micronized formulation was considered the strongest candidate.

9 FINAL FOUR CANDIDATE FORMULATIONS

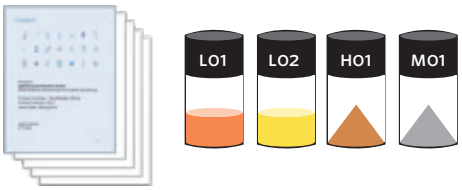
Candidate Formulation	Candidate Formulation #	Drug Loading	Total amount (g)
Lipid based	**1A**	10%	4g
Lipid based	**4A**	2.5%	4g
Solid Dispersion	**HME-6**	20%	3g
Particle Size	**M01**	100%	1g

10 CANDIDATE SCORE EVALUATION

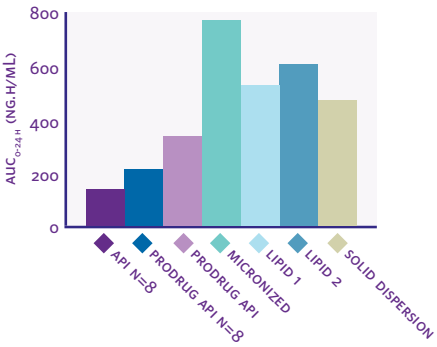
Candidate Formulation	Physical	Chemical	Processability	DCS Fit	Overall
Lipid based 1A	2	2	2	2	**2**
Lipid based 4A	3	3	2	2	**3**
Solid Dispersion HME - 6	1	2	4	2	**3**
Particle Size M01	1	1	1	1	**1**

*1 IS THE HIGHEST & 5 IS THE LOWEST

11 CATALENT DELIVERABLES



12 PK DATA (TRIO)



Preliminary data showed enhanced bioavailability of all 4 formulations compared with the prodrug.

Conclusion

Trio's Medical Director commented:

"Catalent's Optiform® Solution Suite met the 12-week guarantee and provided good choices for candidate formulations with extensive supporting data. The platform represents good value for money based on the other options that we evaluated. Our early PK analysis shows improved AUC from the candidate formulations, but we need to collect data from more subjects and look to further increase AUC".

"Over the years, in my experience of carrying out early phase I studies, large and small, worldwide, the planned start is delayed in about 25% of those studies, mostly due to formulation problems. The majority of small molecules are now coming from small- to medium-sized companies, most of which have to outsource formulation work. They are rarely aware of the potential problems. So, my advice is to start formulation work as early as possible".

.

more products.
better treatments.
reliably supplied.™

Discover more solutions at www.catalent.com/optiform
GLOBAL + 1 888 SOLUTION (765-8846)
EU + 800 88 55 6178
solutions@catalent.com