BDG SYNTHESIS

Certificate of Analysis

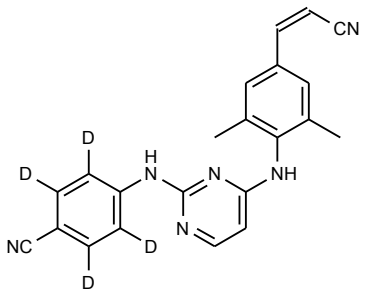
BDG Synthesis certifies that this reference material meets or exceeds the specifications stated herein.

Neil Beare, PhD, Director
22 September 2016

Name: ***Z*-Rilpivirine-d_4**

CAS Number: none

Structure:



Molecular Weight: $C_{22}H_{14}D_4N_6$ = 370.44

Lot Number: BDG 16784.1

Appearance: White, crystalline solid

Corrected Purity: 98.8 % (HPLC) - 1.0 % (water) = 97.8 %

Isotopic Purity: Under 0.5 % d_0

Re-test Date: 22 September 2021

Storage and Handling:

Temperature:	refrigerate for prolonged storage; may be handled and shipped at ambient temperature.
Humidity:	not believed to be hygroscopic; may be handled in normal laboratory atmosphere.
Light:	protect from strong sunlight.
Caution:	only experienced laboratory personnel should handle the material.

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Identity and Purity

Proton NMR Spectrum

Identity: the signals are consistent with the proposed structure and in accord with literature where available.
Isotopic Labelling: signals at the sites of deuteration are greatly diminished, compared with the spectrum of unlabelled material, indicating clean deuteration.
Residual Solvents: no residual solvents are observed.
Impurities: no significant impurities are evident in the spectrum.

Carbon-13 NMR Spectrum

Identity: the signals are consistent with the proposed structure and in accord with literature where available.
Isotopic Labelling: signals at the sites of deuteration have collapsed to small multiplets compared with the spectrum of unlabelled material, indicating clean deuteration.

High-resolution Mass Spectrum (TOF MS ES+)

Found *m/z* 371.1918. $C_{22}H_{15}D_4N_6$ $[M+H]^+$ requires *m/z* 371.1922. The deviation of 1.1 ppm is within normally accepted limits for the establishment of identity by HRMS. No signal for d_0 material was seen (detection limit about 0.5 %).

HPLC

A somewhat broadened, symmetrical peak is observed (98.8 %). A small peak for *E*-Rilpivirine-d_4 is observed (15.47 min). Note: in the absence of reference materials for preparing calibration curves, it is assumed that all peaks have the same detector response. Where possible, the conditions of analysis follow a pharmacopeial or literature method, or have been adapted from same.

Elemental Analysis

	Found:	C 70.66, H 3.75, D 2.14, N 22.70 %
$C_{22}H_{14}D_4N_6 \cdot 0.2H_2O$	Requires:	C 70.64, H 3.88, D 2.15, N 22.47 %, H_2O 0.96 %
$C_{22}H_{14}D_4N_6$	Requires:	C 71.33, H 3.81, D 2.17, N 22.69 %

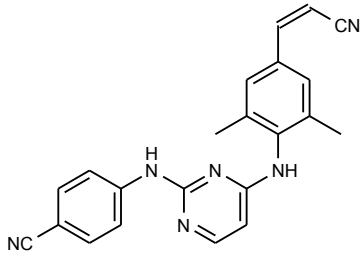
The elemental analyses fall somewhat outside those expected for anhydrous material; the presence of water is reasonably expected from the method of purification and/or the type of material, and the "best-fit" hydrated molecular formula is given. In the absence of a Karl-Fischer water analysis, we recommend that the "best-fit" water content be used when determining corrected purity.

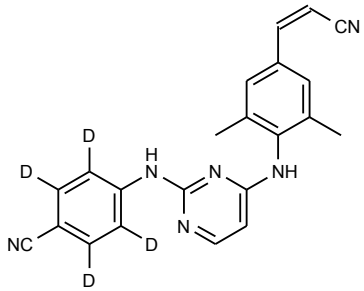
The available quantity of custom-synthesised material is always small, and this limits the extent and type of analytical data which can be obtained. This Certificate is presented in descriptive format for use by analytical chemists who are trained in the use of custom-synthesised materials. Custom materials often contain higher levels of residual solvents and/or water, and we urge you to use the corrected purity where needed rather than the raw HPLC purity. This compound is intended for use as an analytical reference material and it is not for human administration. Structures are shown with relative stereochemistry unless otherwise specified.

The re-test date is assigned from experience gained with the material in the laboratory and/or on storage. It is not possible to perform formal storage studies because of the small amount of material available.

BDG SYNTHESIS

Proton NMR Spectrum of *Z*-Rilpivirine (top) and *Z*-Rilpivirine-d_4 (bottom) in DMSO-d_6





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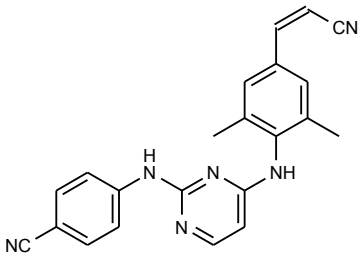
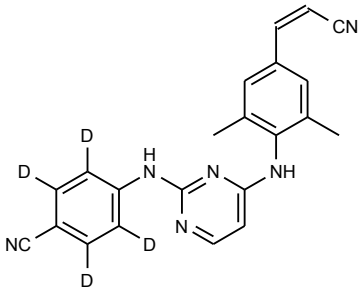
BDG SYNTHESIS

Carbon-13 NMR Spectrum of *Z*-Rilpivirine (top) and *Z*-Rilpivirine-d_4 (bottom) in DMSO-d_6





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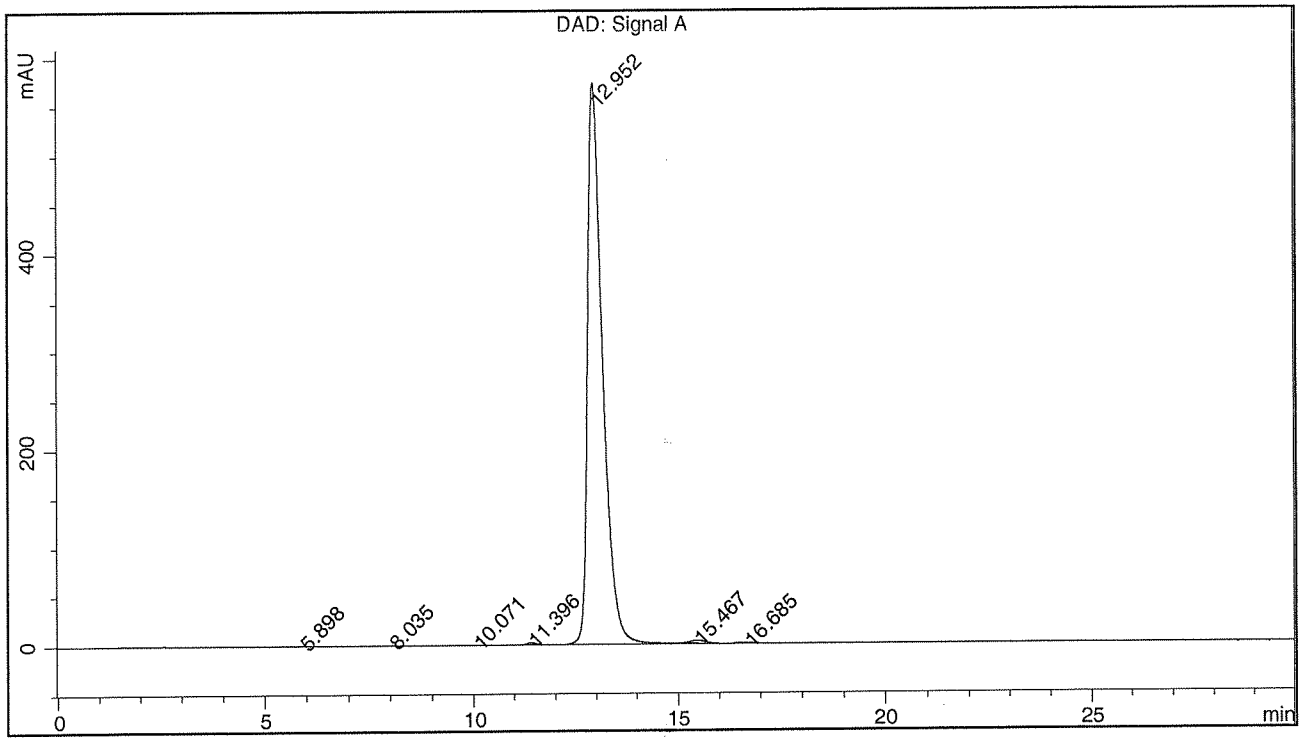
BDG - Analysis of Z-Rilpivirine-d4

Column : Phenomenex Luna C18(2) 5um 250 x 4.6 mm
Guard : Phenomenex Security Guard C18 RP 4 x 3 mm
Mobile Phase : 50:50:0.05 Water : Methanol : Trifluoroacetic Acid
Column Temperature : 30 C . . . . . Flow Rate : 1.0 mL/min . . . . . Injection Volume : 10 uL
Sample Solvent : 1:1 Water : Methanol . . . . . Detection : UV 290 nm

Sample Name	BDG 16784.1	**Instrument**	AnalyticalLC01
Acquisition	22/09/2016, 14:35:49	**Method (rev.)**	LC10678c (15)
Sequence	BDG_22Sep2016a - Reprocessed	**Vial Position**	40
Operator	solvation010\cerityadmin	**Injection**	1 of 1



Area Percent Report

Peak#	RT	Peak Height	Peak Area	Width	Area %
1	5.90 min	0.4435	6.3596	0.1953 min	0.043 %
2	8.04 min	0.5106	10.0517	0.2417 min	0.068 %
3	10.07 min	0.2576	5.0197	0.2433 min	0.034 %
4	11.40 min	2.2490	41.0570	0.2410 min	0.276 %
5	12.95 min	574.1038	14693.4206	0.3826 min	98.828 %
6	15.47 min	3.2415	89.8035	0.4072 min	0.604 %
7	16.69 min	0.7365	21.9223	0.3673 min	0.147 %