Abstract
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IND enabling investigations of MVT-1075, a CA19-9 targeting radioimmunotherapy

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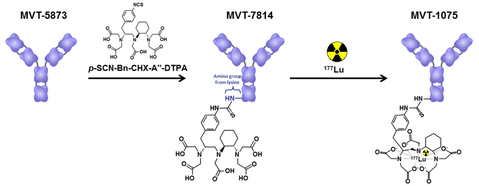
Background

Nomenclature of Products in this Investigation

MVT-5873: native anti-CA19-9 fully human mAb (HuMab-5B1)
MVT-7814: *p*-SCN-Bn-CHX-A"-DTPA conjugated HuMab-5B1
MVT-1075: 177-Lutetium (^{177}Lu) labeled HuMab-5B1

MVT-1075 (^{177}Lu-CHX-A"-DTPA-5B1) is a radioimmunotherapy formed via conjugation of GMP MVT-5873 with the bifunctional chelating agent *p*-SCN-Bn-CHX-A"-DTPA (DTPA) followed by radiolabelling with ^{177}Lu, as shown below:



MVT-1075 preclinical studies have shown anti-tumor efficacy as a radioimmunotherapy and biodistribution studies support the proposed phase I starting dose and clinical design.[1] We report here the preclinical manufacturing optimization and characterization of MVT-1075 that enabled the recent notification by FDA to proceed with an IND application for a first-in-human trial in patients with positive advanced pancreatic cancer and other CA19-9 positive malignancies.

Manufacturing and Characterization Process

The process for combining the DTPA chelator with MVT-5873 to form MVT-7814 was evaluated as a function of reaction conditions and scales to ensure manufacturing scalability and robustness. Process parameters investigated included antibody concentration, ratio to DTPA, conjugation conditions and quenching. Characterization included potency and identity by ELISA, aggregates by SEC, purity by CEX, isoelectric point by iCIF and DTPA:antibody ratio (DAR) by MS.

MVT-7814 Intermediate: GMP MVT-5873 is reacted with DTPA in pH 9.0 sodium bicarbonate. The reaction is quenched and unreacted DTPA is removed by tangential flow filtration into ammonium acetate (pH 7.0). Product is stored < -60˚C in single use vials.

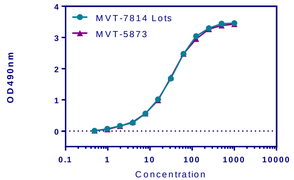
The process for radiolabeling MVT-7814 was evaluated at manufacturing scale to qualify process reproducibility. Radiochemical purity was measured by thin layer chromatography (TLC) using BioDex paper chromatography strips and by HPLC-SEC using a Tosoh TSK-Gel 3000SWXL. Immunoreactivity was measured by a modification of the method by Lindmo[2] using sialyl Lewis A (sLe^a) coated magnetic beads in place of cells.

Clinical grade MVT-1075: Single-use drug product was manufactured by radiolabelling MVT-7814 with ^{177}LuCl to produce MVT-1075. The final product is buffer exchanged into formulation buffer using sterilized PD-10 columns to produce a single-use vial.

MVT-7814 Characterization & Process Reproducibility

Confirmation of Target Binding by ELISA (overlay of 3 lots with MVT-5873)

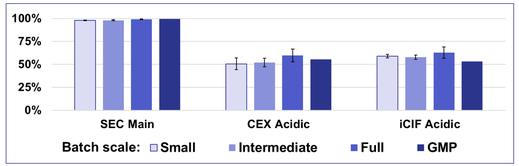
- ELISA is used to assess binding of product to the sLe^a target
- MVT-7814 binding is comparable to MVT-5873
- DTPA conjugation does not interfere with antibody binding
- Multiple batch analysis demonstrates manufacturing process reproducibly



Confirmation of DTPA Conjugation Reproducibility by SEC, CEX, iCIF and MS

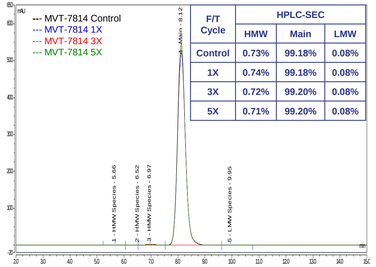
MVT-7814 manufacturing process reproducibility was assessed for aggregates, charge variants and modification by SEC, CEX, iCIF and semi-quantitative MS, respectively.

- DTPA conjugation does not increase aggregate levels
- Charge and pI variant profiles were reproducible and comparable across scales
- Mass spectrometry demonstrates DTPA conjugation to the heavy chain with a chelator:antibody ratio of approximately 0.5 (data not shown).



MVT-7814 Stability Over Five Freeze Thaw Cycles

- MVT-7814 single use vials are stored at < -60˚C prior to ^{177}Lu radiolabeling
- MVT-7814 freeze-thaw stability was characterized by SEC analysis.
- No increases in aggregate or low molecular weight species were observed after 5 cycles.
- These data demonstrate suitability of the MVT-7814 product formulation to support manufacture of clinical grade MVT-1075.



F/T Cycle	HPLC-SEC		
	HMW	Main	LMW
Control	0.73%	99.18%	0.08%
1X	0.74%	99.18%	0.08%
3X	0.72%	99.20%	0.08%
5X	0.71%	99.20%	0.08%

MVT-1075 Manufacturing Qualification

- MVT-1075 qualification lots were generated and characterized by IsoTherapeutics Group
- Specifications included radiochemical purity and immunoreactive fraction
- Data demonstrate reproducibility of the manufacturing process
- MVT-1075 product lots consistently meet prospective acceptance criteria and are suitable for clinical use

Test	Lot 1	Lot 2	Lot 3	Lot 4	Lot 5
Radiochemical Purity (%)	99	98	99	100	100
Immunoreactivity (%)	116	98	124	122	110
SEC (LMW) (%) Radiochemical	0.4	ND	ND	0.1	ND
SEC (Main) (%) Radiochemical	99	98	100	99	99
SEC (HMW) (%) Radiochemical	0.4	ND	ND	0.5	0.6

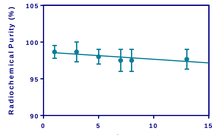
ND, Not Detected

MVT-1075 Drug Product Stability

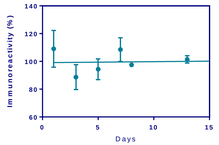
- MVT-1075 drug product distribution includes storage and shipment <-15ºC for delivery to the clinical pharmacy and ambient temperature storage prior to patient use
- Samples were stored less than -15ºC for 13 days (~ two ^{177}Lu half-lives) and then thawed and stored on day ambient conditions (14 days total)
- The product critical quality attributes evaluated included maintenance of radiolabeled product integrity and target binding.
- Radiochemical purity was assessed using iTLC to measure free ^{177}Lu in the presence of the radioimmunotherapy product
- Immunoreactivity of MVT-1075 was assessed by a modified Lindmo assay[2] using sLe^a coated beads

iTLC Radiochemical Purity Confirms MVT-1075 Maintains ^{177}Lu Labeling

- The 13-day study demonstrated that ^{177}Lu is not released from MVT-1075 product
- Radiochemical purity was >98%
- Three MVT-1075 lots are shown as average values ± S.E.M.



Immunoreactivity Confirms MVT-1075 Maintains sLe^a Target Binding

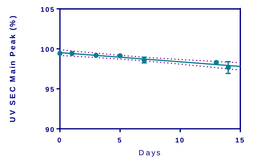


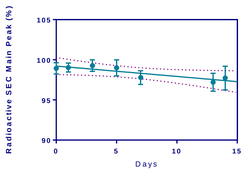
- The 13-day study demonstrates that MVT-1075 drug product maintains sLe^a binding in formulation buffer under the proposed clinical storage and distribution conditions
- Immunoreactivity was 99.9% ± 3.3%
- Three MVT-1075 lots are shown as average values ± S.E.M.

MVT-1075 Formulation Stability (continued)

MVT-1075 Product Formulation Limits Aggregation and Degradation

- Samples were analyzed by SEC with detection by UV and radiochemical decay
- Product purity remained greater than 97% monomer during the 14 day study
- Labeling with ^{177}Lu did not result in higher order aggregates or antibody degradation products
- Three MVT-1075 lots are shown by the solid trend line with a 95% confidence interval





MVT-1075 Serum Stability

- Three lots of MVT-1075 drug product were evaluated for stability in human serum at 37˚C over 13 days as a surrogate for clinical conditions
- Radiochemical purity and immunoreactivity were measured at release and four timepoints
- The study demonstrates suitability of MVT-1075 drug product for clinical investigation

Test	Day				
	0	3	5	7	13
Radiochemical Purity (%)	99 ± 0.2	96 ± 2%	92 ±1	87 ± 2%	70 ± 4
Immunoreactivity	113 ± 4	93 ± 6	63 ± 0.5	77 ± 4	112 ± 31

Conclusions

- MVT-1075 is reproducibly manufactured in a two step process to a high quality product suitable for clinical administration
- MVT-7814 manufacturing conditions maintain antibody affinity & integrity measured by sLe^a binding, absence of aggregates, charge isoform reproducibility and antibody to DTPA ratio
- MVT-1075 manufacturing conditions consistently yield drug product suitable for clinical use
- MVT-1075 formulation and serum stability profiles support clinical use
- MabVax has received FDA authorization for IND130813 to proceed with a phase I clinical trial for the treatment of patients with pancreatic ductal adenocarcinoma and other CA19-9 positive malignancies

References
1. Houghton JL, et al. AACR Annual Meeting 2017, abstract 5204/22
2. Lindmo, T., et al. *J Immunol Methods*, 1984. 72(1): p. 77-89.

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