Thymosin Alpha-1 (Ta1) Related Bulk Drug Substances

Pharmacy Compounding Advisory Committee Meeting

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Elizabeth Hankla, PharmD
Senior Clinical Analyst
Pharmacy Compounding Review Team (PCRT), Office of Specialty Medicine (OSM), Office of New Drugs (OND)
and
Jing Li, PhD
Chemist
Office of Pharmaceutical Quality Assessment II (OPQAII), Office of Pharmaceutical Quality (OPQ)

Center for Drug Evaluation and Research (CDER), FDA

Ta1 Evaluation Team

Jing Li, PhD, OPQAII, OPQ

Russel Wesdyk, BS, MBA, OPQAII, OPQ

Nga-Lai Poon, PharmD, Office of Compounding Quality and Compliance (OCQC), Office of Compliance (OC)

Kemi Asante, PharmD, MPH, RAC, OCQC, OC

Edna Albuquerque, PhD, Division of Pharmacology/Toxicology, Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine/Specialty Medicine (DPT-RDPRUM/SM), OND

Andrea Benedict, PhD, DPT-RDPRUM/SM, OND

Elizabeth Hankla, PharmD, PCRT, OSM, OND

Emily Kneeream, PharmD, PCRT, OSM, OND

Katie Park, PharmD, MPH, PCRT, OSM, OND

Marianne San Antonio, DO, PCRT, OSM, OND

Madeline Wolfert, MD, PCRT, OSM, OND

Suhail Kasim, MD, PCRT, OSM, OND

Daiva Shetty, MD, PCRT, OSM, OND

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Nomination (1)

- Ta1-related bulk drug substances (BDSs) were nominated for inclusion on the list of BDSs that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (503A Bulks List)
  - The nomination was withdrawn, and FDA is evaluating the substances at its discretion
- Product proposed in the nomination: 3 mg/mL injection for subcutaneous (SC) administration

Nomination (2)

Ta1 (free base) and Ta1 acetate were evaluated for the following uses:

1. Hepatitis B
2. Hepatitis C
3. Human immunodeficiency virus (HIV)
4. Coronavirus disease 2019 (COVID-19)
5. Depressed response to vaccinations; adjuvant to “flu vaccines” (influenza vaccines)
6. Malignant melanoma
7. Hepatocellular carcinoma (HCC)
8. Non-small cell lung cancer (NSCLC)
9. Sepsis
10. Infections after hematopoietic stem cell transplantation (HSCT)
11. Chronic obstructive pulmonary disease (COPD)
12. Myalgic encephalomyelitis and chronic fatigue syndrome (ME/CFS)

Evaluation Criteria

- Physical and chemical characterization
- Historical use in compounding
- Safety
- Available evidence of effectiveness or lack of effectiveness

Summary of Basic Information on Ta1 Free Base and Ta1 Acetate

	Ta1 (free base)	Ta1 Acetate
UNII Code	W0B22ISQ1C	Not available
CAS No.	62304-98-7	Uses the CAS number of the free base
MF/MW (g/mol)	$C_{129}H_{215}N_{33}O_{55}$/3108.3	$C_{129}H_{215}N_{33}O_{55} \cdot xCH_3COOH$/NA
Chemical Structure	Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn-OH	Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn-OH x·CH_3COOH
Supplier	Yes	Yes
Active Moiety	Ta1 (free base)	Ta1 (free base)

CAS = Chemical Abstracts Service; MF = molecular formula; MW = molecular weight

Summary of Information Submitted in The Withdrawn Nomination

Nominated BDS	Thymosin Alpha-1 (Ta1)
BDS per UNII code	W0B22ISQ1C *(matches Ta1 free base)*
Certificate of Analysis (CoA)	CoA provided for Ta1 Acetate
CAS No.	62304-98-7 *(matches Ta1 free base)*
MF	$C_{129}H_{215}N_{33}O_{55}$ *(provided in the CoA that matches Ta1 free base)*
MW (g/mol)	3108.3 *(provided in the CoA that matches Ta1 free base)*
Chemical Name	Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn-OH *(matches Ta1 free base)*
Active Moiety in Clinical References	Ta1 free base

Italics in the table above represents the information identified by the FDA.

Physical and Chemical Characterization (1)

Ta1 (Free Base)

- A N-terminal acetylated 28 amino acid peptide:
  - Originally isolated from thymosin fraction-5 of calf thymus in 1977
  - Chemically produced Ta1 (free base), named thymalfasin, which is identical in amino acid sequence to natural Ta1 (free base)
- White to off-white lyophilized powder
- Solubility in water up to 2 mg/mL
- No USP drug substance monograph
- BDS Storage and Stability:
  - It is recommended to be stored desiccated below - 18°C; upon reconstitution, Ta1 (free base) in solution is stable between 2 - 7 days at 4°C and for future use below - 18°C
  - Sensitive to product formulation, process and environment conditions which may lead to aggregation and degradation

Physical and Chemical Characterization (2)

- Potential for Impurities
  - Peptide-related impurities and peptide synthesis process-related impurities (e.g., starting materials, residual solvents, coupling reagents, activators, catalysts)
- Potential for immunogenicity
  - No CoA for Ta1 free base in the nomination
  - No information on impurity limits/testing results as critical attribute control in the CoA reported from public domain
  - Lack of information on the potential of peptide aggregation, especially when formulated in an injectable dosage form for SC administration

Conclusion: Ta1 (free base) is not well-characterized

- Lack of certain critical characterization data, such as impurities, aggregates, bioburden/bacterial endotoxin levels
- Potential for immunogenicity when formulated in an injectable dosage form for SC administration due to potential for aggregation as well as peptide-related impurities
- The proposed concentration for injectable product (3 mg/mL) is greater than the solubility of Ta1 (free base) in water (2 mg/mL). No information was provided regarding how a greater solubility is achieved

Physical and Chemical Characterization (3)

Ta1 Acetate

- Acetate salt form of Ta1
- White to off-white lyophilized powder
- No USP drug substance monograph
- BDS Storage and Stability
  - Manufacturer recommends storage in a sealed container at 2°C to 8°C in a refrigerator or freezer
  - Ta1 acetate is publicly reported to remain stable when stored in a freezer under - 20°C
  - Sensitive to product formulation, process and environment conditions which may lead to aggregation and degradation
- Impurities
  - Peptide-related impurities and peptide synthesis process-related impurities (e.g., starting materials, residual solvents, coupling reagents, activators, catalysts)

Physical and Chemical Characterization (4)

- Potential for immunogenicity
  - CoA provided includes identification, assay, water content, and acetate content, but no testing results for the control of impurities and aggregates
  - Literature search could not find other CoAs nor other information to evaluate potential single impurity and total impurity limits
- Solubility in water up to 1 mg/mL

Conclusion: Ta1 acetate is not well-characterized

- Lack of certain critical characterization data, such as impurities, aggregates, bioburden/bacterial endotoxin levels
- Potential for immunogenicity when formulated in an injectable dosage form for SC administration due to potential for aggregation as well as peptide-related impurities
- It is difficult to compound Ta1 acetate when reconstituting it using water as the solvent due to its limited water solubility

Historical Use in Compounding (1)

- The earliest and extent of Ta1 (free base) or Ta1 acetate use in compounding is unknown
- No evidence of compounded drug products containing Ta1 (free base) or Ta1 acetate in the published literature or in outsourcing facility reports
- Compounded drug products containing Ta1 are marketed online in the United States:
  - As an injectable and nasal spray
    - A website advertises a compounded SC injectable product that is “FDA-approved”; however, FDA has approved no drug products containing Ta1
  - For use in conditions such as including hepatitis B, hepatitis C, HIV, chronic fatigue, inflammation, sepsis, COVID-19, Lyme disease, allergies, cancer, asthma, COPD, and psoriatic arthritis

Historical Use in Compounding (2)

- According to the SciClone Pharmaceuticals'[1] 2014 Annual Report, Ta1 is "approved" for use in countries in the Asia-Pacific region, Latin America, Eastern Europe, and the Middle East (e.g., treatment of hepatitis B and C, as a vaccine adjuvant, and chemotherapy adjuvant)
  - FDA is unable to independently verify these claims of approval in all the specified countries
- Ta1 is not approved in the United States, Japan, or Europe (except Italy)
- Ta1 is not recognized in the European or Japanese Pharmacopoeias

[1] SciClone Pharmaceuticals is a pharmaceutical company that funds studies associated with the development of its product Zadaxin (Ta1 (free base)), 1.6mg solution for injection.

Nonclinical - Safety (1)

A product monograph for Zadaxin (Ta1 free base 1.6 mg/mL) (SciClone Pharmaceuticals) provides high-level summaries of the nonclinical findings listed below. However, it does not include the underlying data for review.

- Acute toxicity: A single SC injection of Ta1 (up to 20 mg/kg) generated no drug-related safety signals in mice, rats, and marmosets
- Repeat-dose toxicity: SC treatment of mice, rats, and marmosets with up to 6 mg/kg/day for 13 weeks or up to 1 mg/kg/day for 26 weeks generated no drug-related safety signals
  - Based on body surface area, the highest tested SC dose (1 mg/kg/day) administered for the longest time (26 weeks) to mice, rats, and monkeys provides safety margins of ~3-fold, 6-fold, and 12-fold to the daily human SC dose of 1.6 mg, respectively
- Genotoxicity: Ta1 did not produce genotoxicity signals in in-vivo and in-vitro assays

Nonclinical - Safety (2)

- Reproductive and developmental toxicity: Per Tuthill (2007), SciClone Pharmaceuticals "successfully completed" a "lengthy Segment 3 Reproductive Toxicology" study in rodents. However, FDA did not identify published studies with the data
- Carcinogenicity: Studies with Ta1 (free base) or Ta1 acetate were not identified

Conclusion:

- Summaries available in a product monograph for Zadaxin (Ta1 free base, 1.6 mg/mL) appear to suggest that Ta1 (free base) did not induce safety signals in nonclinical toxicity studies
  - The underlying nonclinical data are **not** included in the monograph for review
- FDA did not identify published nonclinical toxicity studies to inform safety considerations for potential clinical uses of Ta1 acetate

Pharmacology

- Ta1 has immunomodulatory properties mediated at least in part by its interactions with Toll-like receptor 9 (TLR9) on dendritic and lymphoid progenitor cells

- According to published nonclinical studies: (i) Ta1 suppressed tumor growth, suppressed viral infections, and decreased sepsis in in-vivo rodent models, and (ii) as a post-treatment, Ta1 increased the antibody titer generated by some vaccines in mice
  - Most studies used fixed doses of Ta1-related substances that, according to the body surface area, translate to human equivalent doses markedly higher than the SC doses of Ta1 used in most clinical studies
  - Difficult to determine the minimal Ta1 dose required to induce a pharmacological response due to lack of studies assessing dose-response relationships

Pharmacokinetics (PK)

Nonclinical:

- In rats that received an intravenous (IV) injection of Ta1 (~0.175 mg/kg), the half-life of the peptide ranged from 1.9 to 3 minutes (Wang et al. 2018; Shen et al. 2019)
- The nonclinical PK profile of Ta1 (free base) or Ta1 acetate delivered via the nominated route of administration (SC) is unknown at this time

Clinical:

- After SC administration in healthy men (900 µg/m^2) (Rost et al. 1999):
  - Ta1 was absorbed rapidly with a T_{max} of approximately 2 hours and a serum half-life of ~2 hours
  - After daily dosing for 5 days, there was no evidence of accumulation and PK parameters resembled those calculated for single dose kinetics

Clinical Safety - FDA Adverse Event Reporting System (FAERS)

- *One* adverse event (AE) report from 46-year-old male receiving peginterferon alpha-2a (PEG-INF) 180 µg SC once per week and Ta1 1.6 mg SC twice weekly for ~12 weeks as part of a clinical trial
  - Subject was hospitalized with anxiety, atrial fibrillation, and a "transient decrease in his TSH [thyroid-stimulating hormone] levels"
  - Interpretation of causality is confounded by concurrent use of PEG-INF as these are potential AEs described in the labeling for PEG-INF

Clinical Safety - Clinical Studies (1)

- Ta1 has been administered in daily doses ranging from ~1-16 mg, usually via SC administration on a biweekly schedule, for treatment periods ranging from 1 day to 12 months
  - Most common dose in clinical studies 1.6 mg via SC route of administration (ROA)
- Most common AEs reported include local irritation, redness, and injection site discomfort (Dominari et al. 2020; Tao et al. 2023)

Clinical Safety - Clinical Studies (2)

- AEs reported in studies:
  - Alanine aminotransferase (ALT) flares in subjects with chronic hepatitis B virus infection (Iino et al. 2005)
  - TSH abnormalities in subjects with chronic hepatitis C virus infection (Sherman et al. 1998)
  - Nipple pain (Gish et al. 2009)
  - Fatal immune hemolytic anemia and engraftment failure in HSCT recipients (Perruccio et al. 2010)

Clinical Safety - Clinical Studies (3)

- Potential safety concerns with administering Ta1 in patients who are undergoing deliberate immunosuppression
  - For example, Ta1 could cause or worsen acute or chronic graft-vs-host disease (GVHD) and lead to engraftment failure in HSCT recipients
- Use as a vaccine adjuvant to influenza vaccines - safety data are insufficient to assess the optimal Ta1 dose and regimen or associated risks
  - Adding an immunomodulatory product such as Ta1 to any vaccine could pose unknown safety concerns that warrant further evaluation

Clinical Safety – Foreign Labeling

- Information obtained from labels for Ta1 products marketed outside the United States include warnings and contraindications when used in children, pregnant and lactating women, patients with autoimmune diseases, and immunosuppressed populations
- The label for Indonesia includes information about transient increases in liver enzymes (characterized as flares) and further Ta1 administration

Clinical Safety - Immunogenicity Concerns

- Ta1 is a 28 amino acid peptide
- Peptides may elicit an immunogenic response; this response may be enhanced when peptides are given via the SC ROA
- Ta1 may pose a significant risk for immunogenicity, potentially amplified by aggregation as well as potential peptide-related impurities
  - The nomination did not include, and FDA is not aware of, information about Ta1 to suggest that this substance does not present these risks
  - We are unaware of data in humans to support the proposed 3 mg/mL strength product, and it is possible that a **more concentrated solution** could lead to **aggregation** and therefore increased immunogenicity potential

Overall Conclusion on Clinical Safety

- In most clinical studies, Ta1 has not been associated with significant adverse events attributable to Ta1 when administered in doses in the range of 1-16 mg via the SC ROA for up to 12 months
  - Most common adverse reactions reported- local irritation, redness, or discomfort at the injection site
- Use of Ta1-related BDSs in compounding may raise safety concerns:
  - Patients undergoing HSCT
    - GVHD and/or engraftment failure
  - Ta1 as a vaccine adjuvant to influenza vaccines
    - Data are insufficient to evaluate the risks when used with influenza vaccines licensed for use in the United States
  - As a peptide with 28 amino acids that is administered through the SC ROA, Ta1 may pose a significant risk for immunogenicity, potentially amplified by aggregation as well as potential peptide-related impurities
    - Highest strength identified to date in clinical studies was 2 mg/mL; it is possible a more concentrated solution could lead to aggregation and therefore increased immunogenicity potential

Effectiveness

- Ta1 (free base) and Ta1 acetate were evaluated for the following 12 uses:
    1. Hepatitis B
    2. Hepatitis C
    3. Human immunodeficiency virus (HIV)
    4. Coronavirus disease 2019 (COVID-19)
    5. Depressed response to vaccinations; adjuvant to “flu vaccines” (influenza vaccines)
    6. Malignant melanoma
    7. Hepatocellular carcinoma (HCC)
    8. Non-small cell lung cancer (NSCLC)
    9. Sepsis
    10. Infections after hematopoietic stem cell transplantation (HSCT)
    11. Chronic obstructive pulmonary disease (COPD)
    12. Myalgic encephalomyelitis and chronic fatigue syndrome (ME/CF)

- For the studies considered in the effectiveness section, Ta1 was administered via SC ROA unless otherwise specified

Effectiveness – Hepatitis B (1)

- Hepatitis B virus (HBV) infection can lead to chronic HBV infection (CHB)
- CHB can cause liver damage, cirrhosis, HCC, and death
- In clinical practice, sustained HBV DNA suppression and clearance of HBV surface antigen (HBsAg) are associated with improved outcomes and often used in assessment of therapeutic effect
- Per professional guidelines, current preferred therapies for CHB include:
  - Antiviral agents (nucleos[t]ide reverse transcriptase inhibitors (NrtIs) entecavir (ETV), tenofovir alafenamide (TAF), tenofovir disoproxil fumarate (TDF) (oral))
    - Administered long-term or lifelong
    - 68-90% of patients achieve undetectable HBV DNA levels after 48 weeks of therapy
    - Shown to reduce risk of cirrhosis, decompensated liver disease, HCC
    - ETV, TAF, TDF lower rates of drug resistance
  - Pegylated interferon alpha2a (PEG-IFN) (SC)
    - Administered for finite duration (typically 48 weeks)
    - HBV DNA suppression rates range 8-43% (depending on HBV e antigen (HBeAg)) status and cutoff to define HBV DNA suppression)

Effectiveness – Hepatitis B (2)

Ta1 monotherapy:

- Ta1 up to 1.6 mg administered twice a week for up to 12 months
- 5 studies[1] from 1998-2005 report mixed efficacy results
  - One randomized (R), double-blind (DB), placebo-controlled (PC) study (Mutchnick et al. 1999): no difference in undetectable HBV DNA rates measured 6 months after end of treatment; Ta1 20% vs. placebo 21%
  - Other studies: undetectable HBV DNA rates at follow-up ranged 15 - 30%; undetectable HBV DNA and HBeAg rates ranged 14 - 40%
- Limitations: small study sizes, lack of blinding, HBV DNA assays with limit of detection higher than current standards (i.e., assays used for quantification of HBV DNA were much less sensitive than current assays), and interpretation of older studies complicated by use of composite endpoints (undetectable HBV DNA and HBeAg, or undetected HBV DNA and ALT normalization)

1. Chien et al. 1998; Mutchnick et al. 1999; Zavaglia et al. 2000; Arase et al. 2003; Iino et al. 2005

Effectiveness – Hepatitis B (3)

Ta1 vs. IFN-alpha monotherapy:

- 4 studies[1] from 1996-2006, Ta1 up to 1.6 mg administered twice a week for 6 months, followed up at 12 months
- Authors generally observed higher rates of undetectable HBV DNA with IFN-alpha group at the end of treatment (60-66.7%), but Ta1 group at the end of follow-up (58.8-72.4%)
- HBsAg data were not discussed in publications
- Limitations: small study size, lack of blinding, HBV DNA assays with limited sensitivity or unclear performance characteristics, outdated comparator
  - Standard interferon-alpha (IFN-alpha) products have been discontinued in the United States. PEG-IFN has replaced the use of INF-alpha; it is more effective than INF-alpha with respect to serologic and virologic outcomes with treatment of HBV; PEG-IFN is better tolerated and requires less frequent dosing

1. Andreone et al. 1996; Zhuang et al. 2001; You et al. 2005; You et al. 2006

Effectiveness – Hepatitis B (4)

PEG-IFN vs. PEG-IFN in combination with Ta1:

- 2 studies evaluated PEG-FN vs. PEG-IFN/Ta1 administered for 48 weeks
  - A retrospective study (Song et al. 2011) showed virologic response (defined as HBV DNA < 2,000 IU/mL) at:
    - Week 48: 35% (PEG-IFN) vs. 40% (PEG-IFN/Ta1);
    - Week 96 (follow-up): 14% (PEG-IFN) vs. 21% (PEG-IFN/Ta1)

    Authors noted the response rate was not statistically different between the two treatment arms.
  - A prospective, open label (OL) study (Kim et al. 2012) showed virologic response (defined as HBV DNA <20,000 IU/mL) at:
    - Week 48: 40% (PEG-IFN) vs. 42.3% (PEG-IFN/Ta1);
    - Week 96 (follow-up): 28% (PEG-IFN) vs. 23.1% (PEG-IFN/Ta1)

    Authors concluded that the addition of Ta1 was not superior to PEG-IFN alone in HBeAg-positive CHB patients "on the basis of antiviral efficacy."
- Limitations: small study sizes, study design (e.g., retrospective analysis, OL), lack of blinding, HBV DNA cut-off much higher than current standards (i.e., assays used for quantification of HBV DNA were much less sensitive than current assays used, and unclear whether similar results would be obtained with current, more sensitive assays)

Effectiveness – Hepatitis B (5)

Entecavir (ETV) vs. ETV in combination with Ta1:

- R, OL trial of ETV monotherapy vs. ETV/Ta1 for 52 weeks (Wu et al. 2018)
  - Undetectable HBV DNA rates:
    - Week 52: 64.6% (ETV) vs. 69.6% (ETV/Ta1),
    - Week 104: 87.7% (ETV) vs. 85.5% (ETV/Ta1)
  - HBsAg clearance rates similar between groups at week 52 (0.3%)
  - Per authors: “The results showed that the combination therapy has a similar effect as entecavir monotherapy in aspects of mortality, decompensation rate, HCC incidence, virological response rate, biochemical improvement and liver fibrosis reversibility in the treatment of HBV-related compensated liver cirrhosis patients.”
  - Limited by OL design

Effectiveness – Hepatitis B (6)

Conclusion:

- We have insufficient evidence to determine the effectiveness of Ta1 for the treatment of HBV infection, which has the potential to be a serious and life-threatening condition
- While available published studies report mixed efficacy results of Ta1 monotherapy; we have limited information about its use with, or as an alternative to, current preferred therapies
- Available studies evaluating Ta1 in combination with currently preferred therapies such as PEG-IFN or ETV have demonstrated unclear efficacy and our ability to interpret them are limited by study design
- There are FDA-approved drugs with established efficacy for the treatment of CHB

Effectiveness – Hepatitis C (1)

- Infection with Hepatitis C virus (HCV) can lead to chronic HCV infection (CHC)

- CHC may cause chronic liver disease and lead to cirrhosis, liver failure, HCC, or death

- Treatment goal: achieve virologic cure as evidenced by sustained virologic response (**SVR**). SVR is defined by undetectable HCV RNA in blood several months (usually 12 weeks) after completing treatment
- Treatment:
  - Currently recommended therapies: oral direct-acting antiviral agents (DAAs) daily for 8 - 12 weeks
    - Achieve SVR rates > 90% using only DAAs (with and without RBV)
    - Administration of ribavirin (RBV) with DAAs is recommended in certain situations
  - Older therapies: IFN-alpha, PEG-IFN, RBV

Effectiveness – Hepatitis C (2)

Ta1 monotherapy:

- R, DB, PC pilot study in subjects with CHC (Andreone et al. 1996)
  - No subject cleared HCV RNA at the end of therapy or during follow-up

Ta1 in combination:

- 5 trials of Ta1 in combination with IFN, with and without RBV[1]- OL, no control arms
  - In studies that reported SVR, SVR rates ranged 21.1 to 40%
  - Limited by factors such as: study design, small study size, older assays, limited SVR data
- 1 trial- R, DB, PC trial of Ta1 in combination with PEG-IFN and RBV (Ciancio et al. 2012) reported:
  - SVR: 12.7% (PEG-IFN/RBV/**Ta1**) vs. 10.5% (PEG-IFN/RBV/placebo)
  - Authors stated that, "the addition of thymosin alpha-1 to the standard of care did not increase the on-treatment HCV viral response"

1. Sherman et al. 1998, Rasi et al. 1996, Kullavanijaya et al. 2001, Moscarella et al. 1998, Poo et al. 2008

Effectiveness – Hepatitis C (3)

Conclusion:

- There are insufficient data to establish effectiveness of Ta1 for use in treating HCV infection, which has the potential to be a serious and life-threatening condition
- Achieving SVR is considered a virologic cure of CHC. Ta1 was studied as an alternative to, or in combination with older therapies with lower SVR than currently recommended standard of care, i.e., oral HCV DAA drug combination therapies (for which SVR rates > 90% in many populations)
- There are available FDA-approved therapies with established efficacy for the treatment of CHC

Effectiveness – HIV (1)

- Human immunodeficiency virus type 1 (referred to as “HIV”) is a virus that attacks the body’s immune system
  - Marked reduction in cluster of differentiation 4 (CD4) positive T-cells
- Per professional guidelines, goal is to initiate antiretroviral therapy (ART) as soon as possible to reduce HIV-related morbidity and mortality and reduce transmission risk
- Considerations on endpoints assessing effectiveness:[1]
  - Primary endpoint: sustained HIV viral load suppression
  - Secondary endpoint: changes in CD4+ T cell counts
  - Monitoring lymphocyte subsets other than CD4+ T cell count has not proven clinically useful, therefore not recommended

[1] Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry

Effectiveness – HIV (2)

Ta1 monotherapy:

- OL study; Ta1 x 14 weeks (Schulof et al. 1986)

Ta1 in combination:

- Single arm OL study in 12 subjects who received polyethylene glycolated interleukin-2 + zidovudine (AZT) + Ta1 x 20 weeks (Ramachandran et al. 1996)
- R, C, OL study in 20 subjects who received highly active antiretroviral therapy (ART) + Ta1 or ART alone x 12 weeks (Chadwick et al. 2003)
- Single arm OL study in 20 subjects who received ART + Ta1 x 24 weeks (Chen et al. 2024)

None of these studies showed increases in CD4+ T cell counts when Ta1 was added

Effectiveness – HIV (3)

Ta1 in combination (continued):

- R, OL study in 28 subjects (Garaci et al. 1994)

Group #	Treatment*	Mean CD4+ T Count Pre-Treatment	Mean CD4+ T Count After 12 Months
1	AZT (n=7)	382 ± 61	331 ± 63
2	AZT + INF-alpha (n=7)	396 ± 98	392 ± 140
3	AZT + Ta1 (n=7)	411 ± 84	446 ± 115
4	AZT + INF-alpha + Ta1 (n=7)	309 ± 77	496 ± 230

*Treated for 12 months

- In Group 4, CD4+ T cell counts increased after 12 months with persistence up to 18 months
- Small sample sizes, potential bias from the unblinded study design and the unknown contribution of Ta1 to the immunomodulatory effect when combined with AZT and IFN-alpha limits the interpretability of the data

Effectiveness – HIV (4)

Conclusion:

- There is insufficient evidence to conclude that Ta1 is effective for the treatment of HIV infection
- Studies were not adequately designed (inadequate sample size, use of unapproved products and non-preferred concomitant therapies in the control arm, lack of randomization, limited duration of follow up)
- CD4+ T cell counts and/or laboratory-based immune parameters are not validated surrogate endpoints
- None of these studies demonstrated statistically significant effects on clinical endpoints such as prevention of AIDS-defining illness or death, or on the validated surrogate endpoint of HIV viral load
- There are numerous FDA-approved drug products for the treatment of HIV

Effectiveness - COVID-19 (1)

- COVID-19 is the disease caused by SARS-CoV-2
  - Early: replication of SARS-CoV-2
  - Later: dysregulated immune/inflammatory response to SARS-CoV-2 infection that may lead to further tissue damage and thrombosis
- FDA was not able to find literature that discussed the use of Ta1:
  - In children with COVID-19
  - In adults with COVID-19 in the outpatient setting
- Focus: the use of Ta1 in adults with acute COVID-19 in the hospital setting

Effectiveness – COVID-19 (2)
Meta-analyses

Publication	Results
Liu et al. 2022	No association between Ta1 treatment and mortality
Shang et. al 2023	Ta1 therapy had no statistically significant effect on mortality
Wang et al. 2023	No differences in -Mortality -Length of hospitalization between subjects who did and did not receive Ta1
Soeroto et al. 2023	-Use of Ta1 was associated with a lower mortality rate -Treatment with Ta1 did not reduce the need for mechanical ventilation; nor did it reduce the length of hospital stay
Conclusion: Three of the four meta-analyses concluded that there was no decrease in mortality in subjects treated with Ta1.	

Effectiveness – COVID-19 (3)

Tuthill et al. 2023:

- Prospective trial in 194 adults with end stage renal disease
- Evaluated Ta1 to prevent COVID-19 infection
  - Evaluation of efficacy endpoints had not yet been completed
  - Results were not reported

Wang et al. 2021b and Wu et al. 2023:

- Retrospective cohort studies in adults hospitalized with COVID-19

Effectiveness – COVID-19 (4)

Limitations:

- Small sample sizes
- Deficient study designs (e.g., retrospective, lack of blinding)
- Use of concomitant medications
- Most of the studies were conducted early in the pandemic
- Heterogeneity between studies in the definition of disease severity
- Dose/frequency of Ta1 exposure not consistently reported

Effectiveness – COVID-19 (5)

Conclusion:

- There is insufficient information concerning effectiveness to support use of Ta1 for the treatment of COVID-19
- IDSA (Infectious Disease Society of America), NIH (National Institutes of Health) and WHO (World Health Organization) treatment guidelines do not discuss the use of Ta1 for COVID-19
- There are FDA-approved therapies with established efficacy for treatment of COVID-19

BREAK SLIDE

Effectiveness – Depressed Response to Vaccinations; Adjuvant to "Flu Vaccines" (Influenza Vaccines) (1)

Study Population (Publication)	N	Described Ta-1 Dose/regimen	Monovalent or Trivalent Influenza Vaccine
Elderly subjects (pilot study)* (Gravenstein 1986)	9	0.9 mg/m^2 twice weekly for 5 weeks **after** vaccination	Influenza seasonal trivalent
Elderly male veterans (Gravenstein 1989)	90	0.9 mg/m^2 twice weekly for 4 weeks **after** vaccination	Influenza seasonal trivalent
Elderly male veterans* (McConnell 1989)	330	0.9 mg/m^2 twice weekly for 2 or 4 weeks **after** vaccination	Influenza seasonal trivalent
Patients with end stage renal disease on hemodialysis (Shen 1990)	97	0.9 mg/m^2 twice weekly for 4 weeks **after** vaccination	Influenza H1N1 monovalent
Patients with end stage renal disease on dialysis (Carraro 2012)	99	0.9;3.2;6.4 mg/m^2, one dose 7 days **before** vaccination and another dose on the **same day** of vaccination	Influenza H1N1 monovalent (Focetria**)

*Abstracts retrieved only, and full-length texts not available

** Not approved for use in the US

Effectiveness – Depressed Response to Vaccinations; Adjuvant to "Flu Vaccines" (Influenza Vaccines) (2)

Limitations:

- Most of the studies did not evaluate appropriate measures of the immune responses
  - ELISA, which is not a measure of clinical effectiveness, was used to evaluate immune responsiveness in 4 of the 5 studies
- Studies had exploratory design, without formal hypothesis testing and prespecified immunogenicity or efficacy endpoints
  - Gravenstein et al. (1986) and McConnell et al. (1989) lacked sufficient detailed information as they were available only in abstract form
- Control groups were missing, or inadequate and data quality were difficult to interpret
  - Studies of Ta1 in the elderly did not use influenza vaccines that are recommended in the US as a comparator (Fluzone High Dose and Fluad)
- Statistical analyses were either not performed or performed on an inappropriate immune response and were descriptive in nature

Conclusion:

- There is lack of sufficient evidence to determine any conclusion on the effectiveness of Ta1 as a vaccine adjuvant
- There are FDA-approved vaccines that include adjuvant components that address the same medical conditions as proposed for the Ta1 compounded drug product

Effectiveness - Malignant Melanoma (1)

- Exploratory, multicenter, OL, R study in 488 patients with stage IV melanoma and unresectable metastases (Maio et al. 2010)
- Primary endpoint- best overall response rate (ORR) at 12 months

Group #	Treatment*	ORR (%)
1	DTIC+IFN-alpha+Ta1 (1.6 mg) (n=97)	7.2
2	DTIC+INF-alpha+Ta1 (3.2 mg) (n=97)	10.3
3	DTIC+INF-alpha+Ta1 (6.4 mg) (n=98)	6.1
4	DTIC+Ta1 (3.2 mg) (n=99)	12.1
5	DTIC+INF-alpha (control group) (n=97)	4.1

DTIC = dacarbazine
*Treatment repeated every 4 weeks; max 6 cycles

- **Failed** to show a significant difference in the ORR with any Ta1 containing regimens compared to the control group
- Study was conducted when chemotherapy and INF or IL-2 were standard of care therapy
  - These therapies are rarely, if ever, used in current clinical practice

Effectiveness - Malignant Melanoma (2)

- Single arm study in 46 subjects with metastatic melanoma who received DTIC + Ta1 + interleukin-2 (IL-2) (Lopez et al. 1994)
- Single arm study in 26 subjects with unresectable metastatic melanoma who received DTIC + Ta1 + INF-alpha (Rasi et al. 2000)
- Retrospective review in subjects with unresectable metastatic melanoma who received Ta1 and ipilimumab (Danielli et al. 2018)

Limitations:

- Single arm studies in which patients received Ta1 in combination with DTIC and INF-alpha or IL-2 (Lopez et al. 1994; Rasi et al. 2000)
- Retrospective design and heterogeneity of patients (Danielli et al. 2018)

Effectiveness - Malignant Melanoma (3)

Conclusion:

- Studies investigating the use of Ta1 in melanoma to date are insufficient to demonstrate the effectiveness of Ta1
- Published studies use control data from inferior, outdated regimens (chemotherapy, INF-alpha)
- Statistically significant, clinically meaningful improvements in Ta1-treated melanoma patients were not demonstrated
- The existence of FDA-approved drugs to treat the disease and the lack of rigorous data demonstrating the benefit of Ta1 for use in patients with malignant melanoma weigh against including Ta1 on the list, particularly in light of malignant melanoma being a serious or life-threatening disease

Effectiveness – HCC (1)

With transarterial chemoembolization (TACE):

- Single arm study in 12 patients with HCC received TACE and Ta1 for 6 months (Stefanini et al. 1998)
  - Limitations: small sample size, single center, single arm design
- R, pilot study in patients with unresectable HCC received TACE plus Ta1 (n=14) or TACE alone (n=11) for 24 weeks (Gish et al. 2009)
  - No difference in the "response rate" (defined as transition to transplant eligibility or lack of disease progression through week 72) or in median overall survival (OS) between the treatment and control groups
  - Designed primarily as a safety study and therefore was not powered for efficacy outcomes

Effectiveness – HCC (2)

After hepatectomy and with TACE to reduce recurrence:

- Single center randomized controlled trial (RCT) in patients with HCC that received hepatectomy plus TACE and Ta1 postop (group A; n=18), hepatectomy plus TACE postop (group B; n=23), or hepatectomy only (group C; n=16) (Cheng et al. 2004)
  - Authors reported:
    - No difference in the one year "recurrent rate" (defined as two of three imaging checks indicating new growth of the tumor at one year)
    - Difference in the median OS (10.0, 7.0, and 8.0 months respectively for groups A, B, and C)
  - Upon reanalysis of the data from this study, a Cochrane Review published in 2011 (Wolf et al. 2011) did not find a statistically significant difference in either OS or disease-free survival (DFS)

Effectiveness – HCC (3)

After hepatectomy to reduce HCC recurrence:

- Three retrospective single center studies (Liang et al. 2016; He et al. 2017; Linye et al. 2021)
- Prospective, non-randomized study in patients with HCC and chronic HBV who were treated with hepatectomy only (n=35) or hepatectomy plus Ta1 and lamivudine postop (n=35) (Cheng et al. 2005)

After liver transplantation to decrease HCC recurrence:

- Retrospective analyses of patients with advanced HCC who received Ta1, sirolimus, and huaier granules (n=18) or tacrolimus-based therapy (n=18) (Zhou et al. 2018)

These studies were limited by their design, and it was not possible to identify the contribution of Ta1 to the observed treatment effect

Effectiveness – HCC (4)

Limitations:

- Retrospective design
- Small patient numbers
- Not adequately designed to assess the study endpoints (e.g., analysis of OS in single arm trials or using descriptive statistics)
- Patients received other therapy in combination with Ta1 and were not designed to demonstrate the contribution of Ta1
- All single center studies except one (Gish et al. 2009)
- Studies were geographically limited
  - 6 studies were conduced in China, 1 in Italy, and 1 in the United States

Effectiveness – HCC (5)

Conclusion:

- There is insufficient evidence to demonstrate the effectiveness of Ta1 as a treatment option for HCC
- In the two RCTs identified to date, authors did not find a difference in the one year “recurrent rate” (Cheng et al. 2004) or “response rate” and median OS (Gish et al. 2009) between the treatment and control groups
- There are no FDA-approved drug products for HCC in the adjuvant setting; however, there are FDA-approved products for the treatment of unresectable HCC

Effectiveness – NSCLC (1)

- R, DB, PC study Ta1 monotherapy for patients with unresectable NSCLC eligible for RT (Schulof et al. 1985). Two different Ta1 dosing schedules (Groups II and III; n=28) compared to a placebo group (Group I; n=13)
  - Study results showed improvements in both relapse-free survival and OS
  - Per authors, "Definitive conclusions regarding the impact of thymosin therapy on survival can only be ascertained in large-scale multi-institutional trials"
- R, OL study ifosfamide chemotherapy (n=10) compared to concomitant ifosfamide + Ta1 + low dose IFN (n=12) for treatment naïve patients with stage III and IV NSCLC (Salvati et al. 1996)
  - Median OS:
    - Ifosfamide chemotherapy = 16 weeks (range 11-63)
    - chemotherapy+Ta1+IFN arm = 24 weeks (range 14-67)
  - It was not possible to identify the contribution of Ta1 to the observed treatment effect

Effectiveness – NSCLC (2)

- OL study; Ta1 monotherapy in patients with previously-treated advanced NSCLC x 1 month (n=10) (Dillman et al. 1987)
- OL study; Ta1 + chemotherapy + interferon (n=56) in patients with treatment naïve and previously-treated stage III and stage IV NSCLC (Garaci et al. 1995)
- Retrospective study limited to studies in Chinese patients with stage IA-IIIA NSCLC (Guo et al. 2021)
- Externally-controlled single arm study conducted in China; Ta1 concomitantly administered with concurrent chemoradiotherapy (Liu F. et al. 2022)
- Meta-analysis limited to studies in Chinese patients with unresectable stage IIIa and IV NSCLC; Ta1 compared to chemotherapy alone control group (Zeng et al. 2019 and Jiang et al. 2011)

Effectiveness – NSCLC (3)

Limitations:

- Randomized controlled trials (Schulof et al. 1985 and Salvati et al. 1996) and single arm studies (Dillman et al. 1987 and Garaci et al. 1995)
  - Small sample sizes
  - Heterogenous populations (e.g., different tumor stages, histology)
  - No information on expressed actionable genomic alterations
  - Lack of adequate comparator to contemporary U.S. standards of care treatment
- Externally-controlled single arm study (Liu F et al. 2022)
  - Study design limitations (e.g., imbalances in measured and unmeasured confounders)
- Systematic reviews and meta-analyses (Zeng et al. 2019 and Jiang et al. 2011)
  - Did not receive U.S. standard of care
  - Not representative of U.S. population with NSCLC
  - Unknown whether Ta1 may provide clinical benefit in current settings

Effectiveness – NSCLC (4)

Conclusion:

- There is insufficient evidence to demonstrate the effectiveness of Ta1 as a treatment option for NSCLC
  - It is unknown whether the addition of Ta1 to contemporary U.S. standards of care treatment regimens would have resulted in clinical benefit for the patients included in the clinical studies
- NSCLC is a serious disease
- There are several FDA-approved drug products for patients with NSCLC

Effectiveness – Sepsis (1)

- Single blind, R, C study (ETASS) in 361 patients with severe sepsis (Wu et al. 2013)
  - In the time-to-event analysis, patients in Ta1 group survived longer after enrollment than the control group
  - 28-day overall mortality 26% Ta1 vs 35% control
  - No significant difference in Intensive Care Unit (ICU) mortality, the length of ICU stay, and duration of ventilation

- Post-hoc analysis of ETASS study (Pei et al. 2020)
  - No results for subpopulation of patients who received Ta1

Effectiveness – Sepsis (2)

- R, C clinical study in septic shock patients (Bai et al. 2022)
  - Ta1 + blood purification + ulinastatin* (n=43)
  - Blood purification + ulinastatin (n=43)
  - Ta1 group showed improvements in immunological and myocardial function
  - No significant difference in survival
    - 11 deaths in Ta1 group and 9 deaths in control group

  Limitations: lack of blinding, small size, and the use of concurrent therapies

- DB pilot study to evaluate the effects of Ta1 on immunomodulation and clinical outcomes in patients with severe acute pancreatitis (n=24) (Wang et al. 2011)
  - Significant reduction in the rate of positive blood and abdominal drainage cultures, and the rate of surgery

*In the United States, ulinastatin is not approved and blood purification is not a standard therapy for sepsis

Effectiveness – Sepsis (3)

Limitations:

- All clinical studies were conducted exclusively in China, where the patient population may not be reflective of the U.S. population
- Treatment of sepsis in China may not be reflective of the U.S. medical practice
- Most studies not double-blinded
- Small study samples
- Short follow-up
- Ta1 used with concomitant therapies

Conclusion:

There is insufficient information to support the effectiveness of Ta1 for the treatment of sepsis. Published clinical trials show that Ta1 may affect biomarkers of immune function; however, the majority do not provide evidence of meaningful clinical benefit of Ta1 in the treatment of sepsis, e.g., reduction in mortality or need for organ support.

Effectiveness – Infections after HSCT (1)

- HSCT can be defined as the transfer of hematopoietic stem cells (HSCs) from one individual to another (allogeneic HSCT) or the re-administration of previously harvested cells to the same individual (autologous HSCT)

- Major causes of early morbidity and mortality for patients who undergo HSCT are disease relapse, acute graft-vs-host disease (aGVHD), infection, regimen related toxicity, and graft failure

- Endpoints that translate to meaningful clinical benefit and survival may include decrease in the infection rate and hematopoietic recovery endpoints (e.g., time to neutrophil recovery in addition to decrease in infection rate)

Effectiveness – Infections after HSCT (2)

- Single arm study in 8 sibling matched and 6 haploidentical HSCT recipients who received 1.6 mg Ta1 daily SC x 16 weeks (Perruccio et al. 2010)
  - Study authors suggest that Ta1 may favorably affect immune function; but larger number of subjects and longer follow-up are needed to assess its impact on survival

- Study in 30 human leukocyte antigen-matched sibling T cell-depleted HSCT recipients who received 1.6 mg Ta1 daily SC x 16 weeks (Perruccio et al. 2011; abstract only)
  - Cumulative incidence of non-relapse mortality reported to be 33% in controls vs 7% in Ta1 treated subjects; but there are limited details in the abstract

- Case series in 7 allogeneic and 1 autogenetic HSCT recipients who received 1.6 mg Ta1 SC twice weekly x 4 weeks (n=4) or standard of care (n=4) (Ding et al. 2013)
  - Infection rate **increased** in Ta1 treated subjects

Effectiveness – Infections after HSCT (3)

Limitations: Heterogenous populations, small sample size, limited duration of follow-up, lack of clinically meaningful endpoints, unclear clinical relevance of the measured markers, missing details relevant to outcomes, etc.

Conclusion: These studies do not provide evidence that Ta1 reduces infections and/or infection related mortality after HSCT.

Effectiveness – COPD (1)

- DB, R trial in 84 patients with acute exacerbation of COPD who received “routine complex treatment” + either Ta1 1.6 mg SC (n=42) or placebo (n=42) x 4 weeks (Jia et al. 2015)
  - Authors state pulmonary function and blood gas indicators improved in both groups but were “more pronounced” in experimental group; however, no details of results were provided

- Study in 122 elderly patients with an acute attack of COPD with respiratory failure who received theophylline sustained release (SR) oral (n=61) or theophylline SR + Ta1 1.6 mg **IV** (n=61) x 4 weeks (Liu et al. 2023)
  - Authors state both groups improved on pulmonary function, blood gas indicators, and exercise ability after treatment with “better effects observed” in the study group

Effectiveness – COPD (2)

Limitations for both studies include:

- Small sample sizes, short duration
- Lack of sufficient details about statistical methodology and other important study design elements (e.g., blinding)
- Lack of meaningful clinical endpoints for the inpatient COPD exacerbation population
- Lack of details on concomitant COPD medications

Conclusion:

Lack of evidence to support the effectiveness of Ta1 for the treatment of COPD. While authors claim that studies suggest that there are “better effects” observed in those who received Ta1 compared to the control group, the available information has limitations as shown in the list above.

Effectiveness - ME/CFS
(Myalgic encephalomyelitis and chronic fatigue syndrome)

FDA did not identify any clinical studies using Ta1 in subjects with ME/CFS.

Conclusion:
FDA did not identify any data to support the effectiveness of Ta1 in the treatment of ME/CFS.

Overall Conclusion on Effectiveness

- Lack of evidence to support the effectiveness of SC Ta1 (free base) and Ta1 acetate for the evaluated uses
- None of the clinical practice guidelines for U.S. health professionals recommend Ta1 (free base) or Ta1 acetate
- Studies on the serious and life-threatening conditions considered in the evaluation of effectiveness of Ta1 were inconclusive and limited by small sample sizes and design deficiencies
- There are multiple FDA-approved drug products indicated for use in the treatment of many of the conditions evaluated

Evaluation Summary

On balance, the physicochemical characterization, information on historical use, lack of evidence of effectiveness, and safety information identified for both Ta1 (free base) and Ta1 acetate weigh **against** them being added to the 503A Bulks List.

In particular, FDA's proposal regarding these substances is based on the fact that Ta1 (free base) and Ta1 acetate:

- Are not well characterized from a physicochemical perspective and it is unclear how it would be possible to formulate the proposed injectable dosage form as an aqueous solution with a concentration of 3 mg/mL
- Insufficient safety information on use of the substances and a lack of information about immunogenicity risks
- Lack of evidence of effectiveness of the substances for use in the conditions evaluated and the existence of FDA-approved drugs to treat most of these conditions, particularly in light of them being serious and/or life-threatening conditions

Recommendation

After considering the information currently available, a balancing of the four evaluation criteria weighs **against** Ta1 (free base) and Ta1 acetate being added to the 503A Bulks List.


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