FDA Briefing Document

Pharmacy Compounding Advisory Committee (PCAC) Meeting

December 4, 2024

The attached package contains background information prepared by the Food and Drug Administration (FDA or Agency) for the panel members of the Pharmacy Compounding Advisory Committee (advisory committee). We are bringing certain compounding issues to this advisory committee to obtain the advisory committee's advice. The background package may not include all issues relevant to the final committee recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Thymosin Alpha-1 (Ta1) – Related Bulk Drug Substances (Ta1 (free base) and Ta1 acetate)

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FDA Evaluation of Thymosin Alpha-1 (Ta1) – Related Bulk Drug Substances (Ta1 (free base) and Ta1 acetate)

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TO: Pharmacy Compounding Advisory Committee

SUBJECT: Evaluation of Thymosin Alpha-1 (Ta1)-Related Bulk Drug Substances (Ta1 (free base) and Ta1 acetate) for Inclusion on the 503A Bulk Drug Substances List

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ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
AE	adverse event
AFP	alfa fetoprotein
AGA	American Gastroenterology Association
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
APASL	Asia-Pacific Association for the Study of the Liver
API	active pharmaceutical ingredient
ARDS	acute respiratory distress syndrome
ART	antiretroviral therapy
ARV	antiretroviral
ASBMT	American Society for Bone and Marrow Transplantation
ASTCT	American Society of Transplantation and Cellular Therapy
AZT	Zidovudine
BCLC	Barcelona Liver Clinic Cancer
BDS	bulk drug substance
BET	bacterial endotoxins test
BID	twice daily
BIW	twice weekly
BP	blood purification
BSA	body surface area
CAERS	CFSAN Adverse Event Reporting System
CCRT	concurrent chemoradiotherapy
CDC	Centers for Disease Control
CFSAN	Center for Food Safety and Nutrition
CHB	chronic hepatitis B
CHC	chronic hepatitis C
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum concentration
CMV	cytomegalovirus
CoA	certificate of analysis
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
DAA	direct-acting antiviral
DB	double-blind
DFS	disease-free survival
DHHS	Department of Health and Human Services
DLI	donor lymphocyte infusion
DTIC	dacarbazine
EASL	European Association for the Study of the Liver
ECMO	extracorporeal membrane oxygenation
ELISA	enzyme-linked immunosorbent assay

EMA	European Medicines Agency
ETV	entecavir
FAERS	FDA Adverse Event Reporting System
FD&C	Federal Food, Drug and Cosmetic (Act)
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GMR	geometric mean titer ratio
GMT	geometric mean titer
GP	cisplatin
GRAS	generally recognized as safe
GVHD	graft-versus-host disease
HAART	highly active antiretroviral therapy
HAI	hospital-acquired infection
HBeAg	hepatitis B (virus) e antigen
HBsAb	hepatitis B (virus) surface antigen antibody
HBsAg	hepatitis B (virus) surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HI	hemagglutination inhibition
HIV	human immunodeficiency virus
HRT	hypofractionated radiation therapy
HSCT	hematopoietic stem cell transplantation
HTLV-III	human T-helper cell lymphotropic retrovirus
IDO	indoleamine-2,3-dioxygenase
ICU	intensive care unit
IDAS	Infectious Diseases Society of America
IFN	interferon
IM	intramuscular
IL	interleukin
INSTI	integrase strand transfer inhibitor
IP	intraperitoneal
IPS	International Peptide Society
ITT	intent-to-treat
IV	intravenous
JAK	Janus kinase
LA-NSCLC	locally advanced non-small cell lung cancer
LOQ	limit of quantification
LPS	lipopolysaccharide
ME-CFS	myalgic encephalomyelitis and chronic fatigue syndrome
MHV	major histocompatibility complex
mHLA-DR	monocyte human leucocyte antigen-DR
MN	microneutralization
MV	mechanical ventilation

NASH	nonalcoholic steatohepatitis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NF	National Formulary
NIH	National Institutes of Health
NK	natural killer (cell)
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NS	nonstructural protein
NSCLC	non-small cell lung cancer
NT	neutralization titer
OF	outsourcing facility
OL	open-label
ORR	overall response rate
OS	overall survival
PaO2	arterial blood oxygen partial pressure
PBMC	peripheral blood mononuclear cell
PC	placebo controlled
PD-1	programmed cell death 1
PEG	pegylated
PEM	postexertional malaise
PFS	progression-free survival
PI	protease inhibitor
PK	pharmacokinetics
PP	per-protocol
PSM	propensity score matched
QOL	quality of life
R	randomized
ROA	route of administration
RCT	randomized controlled trial
RR	risk ratio
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SC	subcutaneous
SF-36	Short-Form 36-Item Health Survey
SOFA	Sequential Organ Failure Assessment
SpO2	oxygen saturation
SVR	sustained virologic response
$T_{1/2}$	half-life
TACE	transarterial chemoembolization
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
Th	T-helper cell

TIM-3	T-cell immunoglobulin and mucin domain-containing molecule-3
TK	toxicokinetic
T_{max}	time to maximum concentration
TLR	Toll-like receptor
TNF	tumor necrosis factor
TNM	tumor-node-metastasis
TSH	thyroid-stimulating hormone
UK	United Kingdom
USP	United States Pharmacopeia
WHO	World Health Organization

I. INTRODUCTION

FDA received a nomination for thymosin alpha-1-related bulk drug substances for inclusion on the list of bulk drug substances (BDSs) that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[1] The nominator of thymosin alpha-1-related BDSs provided inconsistent information in the nomination package regarding the specific BDS proposed. Specifically, it is unclear whether the nomination was for thymosin alpha-1 (Ta1) (free base) or Ta1 acetate. Ta1 (free base) and Ta1 acetate are different BDSs. Please see additional information in section II.A. The nomination was withdrawn[2], and FDA is evaluating the substances at its discretion.

Peptides, such as Ta1, have specific considerations that differentiate them from small molecule drugs due to their composition, which may include immunogenic potential, peptide self-association and aggregation, the potential for peptide-related impurities, and challenges in characterization. Although it is unclear whether the nominator intended to nominate Ta1 (free base) or Ta1 acetate, due to FDA's significant safety concerns related to the use of certain peptides in compounded drug products, FDA has decided to evaluate both on its own initiative.

We evaluated Ta1 (free base) and Ta1 acetate for the following uses:[3,4]

Hepatitis B	Hepatocellular carcinoma (HCC)
Hepatitis C	Non-small cell lung cancer (NSCLC)
Human immunodeficiency virus (HIV)[5]	Sepsis[5]

[1] Nominations that had been submitted include: Nomination from Wells Pharmacy Network thymosin alpha-1 (Document ID: FDA-2015-N-3534-0288) can be accessed at: https://www.regulations.gov/document/FDA-2015-N-3534-0288. This nomination was withdrawn, but because FDA is evaluating Ta1 (free base) and Ta1 acetate on its own initiative, FDA considered information submitted in this nomination as part of this evaluation.

[2] Document ID: FDA-2015-N-3534-0470.

[3] We have explained that it is necessary to evaluate a nominated bulk drug substance in the context of the uses proposed for compounded drug products that include the substance, though we acknowledge that inclusion of a substance on the 503A Bulks List may not be limited to a specific use. See 84 FR 4696, 4701.

[4] Ta1 was nominated for the following additional uses: chemotherapy adjunct, cystic fibrosis, Lyme disease, geriatric immune support, and "chronic inflammatory conditions; autoimmunity." FDA considered its use as a chemotherapy adjunct in the context of the nominated conditions of NSCLC, HCC, and malignant melanoma. FDA did not evaluate the proposed uses of cystic fibrosis and Lyme disease because the nomination did not include sufficient information for the Agency to evaluate whether the substance is appropriate for these uses in compounded drug products. In addition, FDA did not identify clinical studies evaluating the use of Ta1 for cystic fibrosis or Lyme disease. See 80 FR 65765 for the information necessary to fully evaluate a substance for inclusion on the 503A Bulks List. The nominator proposed certain broad uses for Ta1, including geriatric immune support, chronic inflammatory conditions, and autoimmunity. We reviewed the supporting articles provided in the nomination to inform our understanding of these uses and focused our evaluation on specific conditions or diseases identified in the supporting articles that were not already nominated: COPD.

[5] Consistent with its practice, FDA in its discretion opted to evaluate the unnominated uses of sepsis, infections after HSCT, HIV, COVID-19, and ME/CFS. See Final Rule entitled List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act, February 19, 2019 (84 FR 4696, 4701); Notice of Proposed Rulemaking entitled List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act, December 16, 2016 (81 FR 91071, 91075). These are all serious conditions, and FDA has become aware of interest in using Ta1 for these uses.

Coronavirus disease 2019 (COVID-19)[5]	Infections after hematopoietic stem cell transplantation (HSCT)[5]
Depressed response to vaccinations; adjuvant to flu vaccines[6]	Chronic obstructive pulmonary disease (COPD)[4]
Malignant melanoma	Myalgic encephalomyelitis and chronic fatigue syndrome (ME/CFS)[5]

The Ta1 drug product proposed in the nomination is a 3 mg/mL injection for subcutaneous (SC) administration.

There is no applicable United States Pharmacopeia (USP) or National Formulary (NF) drug substance monograph for Ta1 (free base) or its acetate form, and neither is a component of an FDA-approved drug.[7]

We have evaluated publicly available data on the physicochemical characteristics, historical use, safety, and effectiveness in compounding of these substances. For the reasons discussed below, we believe the evaluation criteria ***weigh against*** placing both Ta1 (free base) and Ta1 acetate on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act (503A Bulks List).

II. EVALUATION CRITERIA

A. Is the substance well-characterized, physically and chemically?[8]

As discussed above, this evaluation pertains to Ta1 acetate and Ta1 (free base).

A BDS or active pharmaceutical ingredient (API)[9] used in a drug product may be a free base (i.e., the native molecule) or a salt or an ester of the free base, all of which share the same active

[6] Ta1 was nominated for the use, "Depressed response to vaccinations; adjunct to flu vaccine." For the reasons detailed in Section II.D.5, FDA evaluated it for the use listed above.

[7] Ta1 has four orphan drug designations in the United States. Designation as an orphan drug qualifies sponsors for certain incentives, but it is a separate process from seeking FDA approval or licensure. Drugs for rare diseases must still go through the same rigorous scientific review process as any other drug for approval or licensing. See https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products. Accessed 9/20/2024.

[8] Among the conditions that must be met for a drug compounded using bulk drug substances to be eligible for the exemptions in section 503A of the FD&C Act is that the bulk drug substances are manufactured by an establishment that is registered under section 510 of the FD&C Act and that each bulk drug substance is accompanied by a valid certificate of analysis. Sections 503A(b)(1)(A)(ii) and (iii). A bulk drug substance is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice. Section 501(a)(2)(B).

[9] The terms BDS and active pharmaceutical ingredient (API) are used interchangeably in the compounding context. See 21 CFR 207.3 ("*Bulk drug substance*, as referenced in sections 503A(b)(1)(A) and 503B(a)(2) of the Federal Food, Drug, and Cosmetic Act, previously defined in § 207.3(a)(4), means the same as "active pharmaceutical ingredient" as defined in § 207.1."). An API is defined in FDA regulations at 21 CFR 207.1, which states "*Active pharmaceutical ingredient* means any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or

moiety.[10] Different active moieties are not interchangeable because they can have different safety and efficacy profiles. Similarly, a free base or the various salts or esters of an active moiety are distinct chemical entities, each with a different chemical structure and unique physical/chemical, or pharmacokinetic/pharmacodynamic characteristics. As a result, each may offer distinct properties (e.g., different solubilities, permeability, melting points, stability, or flow characteristics) and may also have different safety and/or efficacy profiles. All distinct active moieties, as well as free bases, salts, or esters of any given active moiety, are distinct BDSs for these reasons.

Ta1 is a N-terminal acetylated 28-amino-acid peptide, originally isolated from thymosin fraction-5 (a crude fraction of the thymus) of calf thymus (Goldstein et al. 1977). The N-terminal Serine modification is performed during synthesis to reduce the overall charge of a peptide. The N-terminal acetylation generates a closer mimic of the native protein. Common names for the BDSs listed in public databases include Ta1, thymalfasin, and Zadaxin.[11]

It is worth noting that thymalfasin is a chemically synthesized version of Ta1. Therefore, Ta1 and thymalfasin can be used interchangeably. However, Zadaxin is a finished drug product available in other countries, which cannot be interchangeably used with Ta1 and thymalfasin. Hence, FDA will only use Ta1 to refer to the proposed BDSs to maintain consistency throughout the memo.

As an initial matter, Table 1 below summarizes the identifying information available in the public domain for each BDS.

prevention of disease, or to affect the structure or any function of the body. Active pharmaceutical ingredient does not include intermediates used in the synthesis of the substance."

[10] "*Active moiety* is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance." 21 CFR 314.3.

[11] https://www.pharmacompass.com/chemistry-chemical-name/thymosin-alpha-1. Accessed 10/31/2024.

Table 1. 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
Molecular Formula/Molecular Weight (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[12]	Yes	Yes
Active Moiety	Ta1 (free base)	Ta1 (free base)

As discussed above, one nomination for Ta1 was submitted and later withdrawn. The nomination provided inconsistent information about the different Ta1 BDSs in the nomination package. Due to inconsistencies in the nomination package, it is unclear which Ta1-related BDS the nominator intended to nominate. For example, the Certificate of Analysis (CoA) submitted with the nomination refers to one BDS by name in the title and a different BDS by the molecular formula/molecular weight. All chemistry-related information about the BDSs provided by nominator is summarized in Table 2.

Table 2. Summary of Information Submitted in the Withdrawn Nomination.

Nominated BDS	Thymosin Alpha-1
BDS per UNII code	W0B22ISQ1C *(matches Ta1 free base)*
CoA	CoA provided for Ta1 Acetate
CAS No.	62304-98-7 *(matches Ta1 free base)*
Molecular Formula	$C_{129}H_{215}N_{33}O_{55}$ *(provided in the CoA that matches Ta1 free base)*
Molecular Weight (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 represent the information identified by FDA.

[12] The existence of a supplier of BDS may be relevant to FDA's characterization analysis because it indicates that consistent production of the BDS according to a standard may be possible. BDSs with suppliers are also frequently accompanied by COAs associated with their production, which can help FDA to identify and characterize BDSs.

FDA is choosing to concurrently evaluate both BDSs, Ta1 (free base) and Ta1 acetate, under two different sub-sections (II.A.1 and II.A.2) and will provide a separate conclusion for each of the two BDSs.

The nominator proposed to compound the BDSs into the following dosage form:

- Injection

For an injection product, critical quality attributes (CQAs) including sterility, bacterial endotoxins test (BET), and foreign particulates are critical safety factors. For this reason, bioburden load (i.e., microbial enumeration test) and BET are considered critical for the BDSs to be used in compounding injections. Evaluation of the solubility of the BDS is also critical to ensure that no precipitates or foreign particulates form in the compounded drug product.

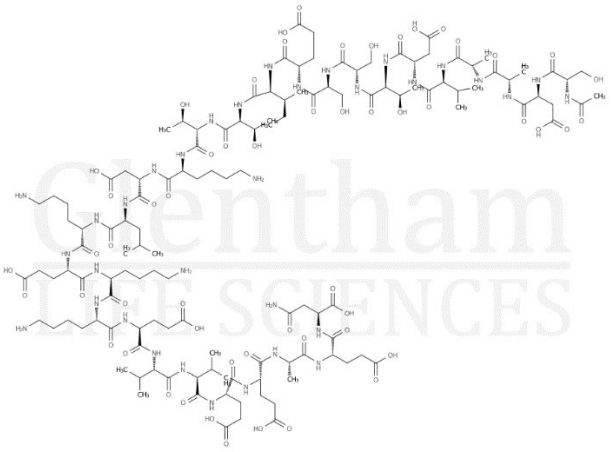
There is no USP drug substance monograph for Ta1 (free base) or its acetate salt form. We reviewed the physical and chemical characterization-related information provided by the nominator and performed a literature search for additional information on Ta1 (free base) and its acetate form. Databases searched for information on Ta1 (free base) and its acetate form in preparation of this section included SciFinder, Analytical Profiles of Drug Substances, PubMed, the European Pharmacopoeia, and the USP-NF.

1. Ta1 (Free Base)

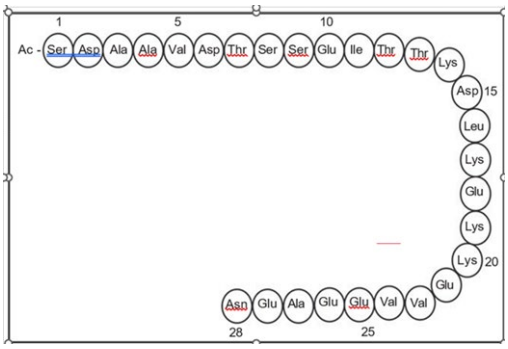
Ta1 (free base) is a N-terminal acetylated 28-amino-acid peptide. It is physiologically present in the human body and was originally isolated from thymosin fraction-5 of calf thymus in 1977 (Goldstein et al. 1977). The solid-phase synthesis method has been developed to chemically produce Ta1 peptide (free base), named thymalfasin, which is identical in amino acid sequence to natural Ta1 (free base).

The molecular formula of Ta1 (free base) is $C_{129}H_{215}N_{33}O_{55}$ and its molecular weight is 3108.3 g/mol. Its chemical structure and peptide sequence are shown in Figure 1. Ta1 (free base) is highly acidic with an isoelectric point of 4.2 because the peptide sequence contains several aspartic amino acids (Asp(s)) and glutamic amino acids (Glu(s)). The nomination did not include a CoA for Ta1 (free base).

Figure 1. Structure (A)[13] and Peptide Sequence (B) of Ta1 (free base).



A: Chemical structure



B: Sequence (Camerini et al. 2015)

a. Stability of the API and likely dosage forms

It is reported that lyophilized Ta1 (free base) is stable at room temperature for three weeks. However, it is recommended to be stored desiccated below -18°C. Upon reconstitution, Ta1 (free base) should be stored at 4°C between 2-7 days, and, for future use, below -18°C. For long-term storage, it is recommended to add a carrier protein (0.1% Human Serum Albumin (HSA) or Bovine Serum Albumin).[14]

FDA notes that peptides, such as Ta1 (free base), can be extremely sensitive to product formulation, process, and environmental conditions (e.g., pH, heat (temperature), concentration, in-process related impurities, excipients), which may lead to the aggregation and degradation of peptides. This could result in loss of their biological activity (Zapadka et al. 2017). Multiple analytical methods may be needed to detect various aggregates, including size exclusion chromatography or field flow fractionation. Such methods involve equipment that may not be available in a compounding facility. Hence, peptides, such as Ta-1 (free base), may require more and/or specific analytical in-process and finished product testing for impurities than what is required for small molecules. Uncontrolled manufacturing processes as well as impurities may increase the risk of product aggregation, especially for Ta1, which has consecutive β-branched amino acids in its structure and a tendency to form β-sheet structures. Significant amounts of aggregates can form in formulated products, especially during storage or when exposed to stress conditions. Therefore, product formulation is critical to the quality and stability of peptide drug products, as it is necessary to maintain the peptide molecules in their native state (in the formulation) to the extent possible.

[13] https://pubchem.ncbi.nlm.nih.gov/compound/Thymalfasin. Accessed 10/31/24.
[14] https://www.prospecbio.com/thymosin_alpha-1. Accessed 10/31/24.

b. Probable routes of bulk drug substance synthesis

As mentioned above, Ta1 (free base) can only be obtained in tiny quantities from the natural source. The solution-based chemical synthesis of Ta1 (free base) has been reported (Birr and Stollenwerk 1979; Wang et al. 1979). Solid-phase synthesis methods were subsequently developed. In 1980, Wong and Merrifield reported improved solid-phase synthesis of Ta1 (free base) (Wong and Merrifield 1980). The synthesis presented in their report illustrates the improvement of the solid-phase synthesis of Ta1 (free base) using aminoacyl-4-(oxymethyl) phenylacetamidomethyl-resin (Pam-resin) instead of a benzhydrylamine resin for attachment through the side chain of asparagine (Asn) as reported by Wang et al. (Wang et al. 1980) to improve the yield. A recent report revealed that combination of the sidechain anchoring approach with the hydrophilicity of the totally PEG-based resin facilitated the synthesis of Ta1 (free base) in high purity and high yields (García-Ramos et al. 2009).

Besides isolation from calf thymus and manufacturing by solid-phase synthesis, Ta1 (free base) was recently reported to be produced via genetic engineering expression of Ta1 (free base) in various hosts, including *Escherichia coli*, *Pichia pastries* and plants (Chen et al. 2005; Chen et al. 2009; Esipov et al. 2010). However, isolation and purification of Ta1 (free base) is reported to be difficult to achieve.

c. Likely impurities[15]

Generally speaking, peptide-related impurities and peptide synthesis process-related impurities contribute to and are considered in the evaluation of impurity profiles for all peptides, including Ta1 (free base). For most synthetic peptides, solid-phase synthesis methods are widely used by industry for peptide synthesis. The solid phase synthesis of peptides may lead to potential peptide-related impurities due to incomplete coupling reactions, truncations, or side reactions. These peptide-related impurities are typically similar in structure to the target peptide and may be difficult to identify and quantify without sophisticated analytical methods. Additional potential common impurities may include starting materials, which typically include protected amino acids, isomeric impurities, free amino acids, and other species that may carry over into the drug substance. In addition, residual solvents, coupling reagents, activators, catalysts, and scavengers may exist as solid phase peptide synthesis process-related impurities. The drug substance and its proposed product-related impurities may also include peptide-related aggregates.

There was no CoA for Ta1 (free base) in the nomination package. We conducted literature searches and found that while CoAs for Ta1 (free base) may contain purity testing results, an

[15] This evaluation contains a non-exhaustive list of potential impurities in the bulk drug substance and does not address fully the potential safety concerns associated with those impurities. The compounder should use the information about the impurities identified in the certificate of analysis accompanying the bulk drug substance to evaluate any potential safety and quality issues associated with impurities in a drug product compounded using that bulk drug substance taking into account the amount of the impurity, dose, route of administration, and chronicity of dosing. When available, nonclinical toxicity data for likely impurities of concern (e.g., nitrosamines, potential mutagenic substances, and potential teratogenic substances) in the nominated bulk drug substance are discussed in the Nonclinical Assessment at Section II.C.1. as part of the safety assessment of the substance.

example of which is shown below (Figure 2),[16] none included information about the impurity limits/testing results in the CoA to demonstrate quality control of the impurity profile of Ta1 (free base).

Because there is a lack of information regarding potential impurities (individual or amount) that can be present in Ta1 (free base) and a lack of information on the potential for peptide aggregation, we cannot rule out the potential for immunogenicity associated with these impurities and peptide-related aggregates of Ta1 (free base), especially when administered by the SC ROA, because this ROA may present a particular risk for immunogenicity.

Figure 2. Example of a CoA for Ta1 (Free Base).

Xi 'an genotide bio-technology Co.,Ltd

Certification of Analysis

Product Name	*thymosin α1*		
Molecular Formula	$C_{129}H_{215}N_{33}O_{55}$	***Batch No.***	
Molecular Weight	*3108.28*	***Manufacturing Date***	
Sequence	**Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Thr-Lys-Asp-L eu-Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn**		

	TEST	***SPECIFICATION***	***RESULT***
1	***Appearance***	*White or slightly yellowish powder*	*Complies*
2	***Identity***	*Monoisotopic Mass: 578.66±1.0*	*3108.4*
3	***Peptide Purity*** *(By HPLC)*	≥98.0%	*98.17%*
4	***Water Content***	<8.0%	*Not test*
5	***Peptide Content*** *(By N%)*	≥80.0%	*83.0%*
6	*Conclusion*	*Conforms to standard*	*Complies*

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Date:Sep-28,2022

d. Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism

Ta1 (free base) is a white to off-white lyophilized powder. Most literature reports indicate that Ta1 (free base) is soluble in water up to 2 mg/mL.[17] This information is consistent with products

[16] https://www.peptidesciences.com/thymosin-alpha-1-10mg. Accessed 11/14/2024.
[17] https://abbiotec.com/peptides/thymosin-alpha-1-peptide. Accessed 10/31/24.

approved in foreign markets and used in the clinical studies referenced in this evaluation, all of which used products at 1.6 mg/mL. However, the nominated strength for the proposed injectable dosage form is 3 mg/mL. Due to its limited solubility in water, it may not be possible to compound the Ta1 (free base) drug product with the concentration of 3 mg/mL proposed in the nomination using water as the solvent.

e. Any other information about the substance that may be relevant, such as whether the bulk drug substance is poorly characterized or difficult to characterize

Because no CoA was provided in the nomination for Ta1 (free base), it is unclear whether a bioburden load (microbial enumeration test) and/or bacterial endotoxin test (BET) is in place to control the microbiological quality of the BDS, proposed for compounding an injectable dosage form. Endotoxin testing is considered a critical quality attribute to control microbiological quality of a BDS intended for an injection product. Also, there is no information about residual solvent testing. No such relevant information about Ta1 (free base) was identified from the public domain.

Conclusions:
Ta1 (free base) is a peptide of 28 amino acids. As reported in the literature, Ta1 (free base) is expected to be stable under storage conditions below -18°C. However, the stability of peptides, such as Ta1 (free base), is highly sensitive to the manufacturing process and quality attributes of the compounded or finished drug product.

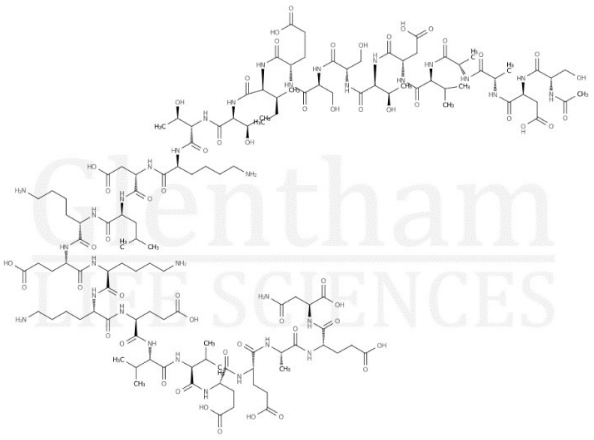
Ta1 (free base) is not well-characterized from the physical and chemical characterization perspective because certain critical characterization data specific to Ta1 (free base), including impurities, aggregates, bioburden, and bacterial endotoxins, were not found in publicly available scientific literature and the nomination package lacked information to establish identity, purity, and impurity profiles of the substance, such as specific tests in COAs. As discussed in Section II.C.2.d., FDA is concerned about the potential for immunogenicity of Ta1 (free base) when formulated in an injectable dosage form for SC administration due to the potential for aggregation as well as potential peptide-related impurities, as discussed in Section II.A.1.c. Injectable routes of administration may present a particular risk for immunogenicity.

In addition, due to limited water solubility of Ta1 (free base), it is unclear how it would be possible to formulate the proposed injectable dosage form with a concentration of 3 mg/mL, and no information was provided to explain how this solubility could be achieved.

2. Ta1 Acetate

The molecular formula of Ta1 acetate is $C_{129}H_{215}N_{33}O_{55} \cdot x(C_2H_4O_2)$, and its chemical structure is shown in Figure 3. The nomination included a CoA for Ta1 acetate with the quality control attribute testing results, including identification, assay, water content, and acetate content (Figure 4). There are no testing results for the quality control attributes on impurities, aggregates, and bioburden load (microbial enumeration test) and/or bacterial endotoxin levels.

Figure 3. Structure[18] of Ta1 Acetate.



$\cdot x(C_2H_4O_2)$

Figure 4. Nominator-Provided Example of a CoA for Ta1 Acetate.

Certificate of Analysis

Thymosin α1 Acetate

Product Name	: Thymosin α1 Acetate	**Lot No.**	: DL5532
Mfg. Date	: Mar 01, 2020	**Exp. Date**	: Feb 28, 2023
M.F.	: $C_{129}H_{215}N_{33}O_{55}$	**M.W.**	: 3108.3
CAS No.	: 62304-98-7	**Batch Qty**	: 315 g
Sequence	: 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		

TESTS	SPECIFICATIONS	RESULTS
Appearance	White to off-white powder	White powder
Identification	3108.3 ± 2	3108.6
Solubility	Soluble in water or 1% acetic acid at a concentration of ≥1mg/mL to give a clear, colorless solution	Conforms
Water Content (KF)	≤ 5.0%	2.3%
Acetate Content	≤ 5.0%	3.3%
Peptide Purity (HPLC)	≥ 96.0%	98.3%
Assay (anhydrous; acetic acid free)	95 - 105%	98.0%
Conclusion: This product is a synthetic peptide and meets the specifications. Long Term Storage: Store in a sealed container at 2°C - 8°C in a fridge or freezer. Distributed by Darmerica.		

98 × 97.7 × 96.7% = 92.

Based on the review of the above information, the lot stands released.

	Name	Title	Signature	Date
Prepared by	Sai Rasane	Quality Assistant		09/17/2020
Released by	Christina Boykin	Quality Assistant		09/17/2020

[18] https://cymitquimica.com/products/3D-FT110250/62304-98-7/thymosin-alpha1-acetate-salt/?srsltid=AfmBOooSqPEtu5L0Hx76CPmmDfcxq1Jwb8SDcZZryg17g_c0bNAxC-Qz. Accessed 10/31/24.

a. Stability of the API and likely dosage forms

Based on the CoA provided by the nominator, long-term storage conditions for Ta1 acetate are "in a sealed container at 2°C to 8°C in a fridge or freezer." Additionally, Ta1 acetate is reported to remain stable when stored in a freezer under -20°C.[19]

FDA notes that peptides such as Ta1 acetate can be extremely sensitive to product formulation, process, and environmental conditions (e.g., pH, heat (temperature), concentration, in-process related impurities, excipients, etc.), which may lead to peptide aggregation and degradation. This could result in loss of their biological activity (Zapadka et al. 2017). Multiple analytical methods may be needed to detect aggregates, including size exclusion chromatography or field flow fractionation. Hence, peptides, such as Ta1 acetate, may require more and/or specific analytical in-process and finished product testing for impurities than what is required for small molecules. Uncontrolled manufacturing processes as well as impurities may increase the risk of product aggregation, especially for Ta1 acetate, which has consecutive β-branched amino acids as shown in the structure and tends to form β-sheet structures. Significant amounts of aggregates can form in formulated products, especially during storage or when exposed to stress conditions. Therefore, product formulation is critical to the quality and stability of peptide drug products, as it is necessary to maintain the peptides in their native state (in the formulation) to the extent possible.

b. Probable routes of bulk drug substance synthesis

Ta1 (free base) can be synthesized using different solid-phase methods as mentioned in II.A.1.b. Then, Ta1 (free base) can be converted into Ta1 acetate.

c. Likely impurities[20]

Generally speaking, peptide-related impurities and peptide synthesis process-related impurities contribute to and are considered in understanding the impurity profile for all peptides, including Ta1 acetate. For most synthetic peptides, solid-phase synthesis methods are widely used by industry for peptide synthesis. The solid-phase synthesis of peptides may lead to peptide-related impurities due to incomplete coupling reactions, truncations, or side reactions. These peptide-related impurities are typically similar in structure to the target peptide and may be difficult to identify and quantify without sophisticated analytical methods. Additional potential common impurities may include starting materials, which typically include protected amino acids, isomeric impurities, free amino acids, and other species that may carry over into the drug

[19] https://lktlabs.com/product/thymosin-%CE%B1-1-acetate/. Accessed 10/31/24.

[20] This evaluation contains a non-exhaustive list of potential impurities in the bulk drug substance and does not address fully the potential safety concerns associated with those impurities. The compounder should use the information about the impurities identified in the certificate of analysis accompanying the bulk drug substance to evaluate any potential safety and quality issues associated with impurities in a drug product compounded using that bulk drug substance taking into account the amount of the impurity, dose, route of administration, and chronicity of dosing. When available, nonclinical toxicity data for likely impurities of concern (e.g., nitrosamines, potential mutagenic substances, and potential teratogenic substances) in the nominated bulk drug substance are discussed in the Nonclinical Assessment at Section II.C.1. as part of the safety assessment of the substance.

substance. In addition, residual solvents, coupling reagents, activators, catalysts, and scavengers may exist as solid phase peptide synthesis process related impurities. The drug substance and its proposed product-related impurities may also include peptide-related aggregates.

In the CoA included in the nomination package, a purity test limit of 95%-105% with the testing result of 98% is listed for Ta1 acetate. However, we note that there are no impurity quality control attribute tests to demonstrate the impurity profiles. We therefore, conducted literature searches and could not find other COAs or other information to evaluate potential single impurity and total impurity limits. Because of the lack of information regarding potential impurities in Ta1 acetate and the potential for peptide aggregation, we cannot rule out the potential for immunogenicity associated with these impurities and peptide aggregates of Ta1 acetate, especially when administered by the SC ROA, because this ROA may present a particular risk for immunogenicity.

d. Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism

Ta1 acetate is a white to off-white solid powder. It is reported to dissolve in water at 1 mg/mL.[21] However, the nominated strength for the proposed injectable dosage form is 3 mg/mL. Due to its limited solubility in water, it may not be possible to compound the Ta1 acetate drug product with the concentration of 3 mg/mL proposed in the nomination using water as the solvent.

e. Any other information about the substance that may be relevant, such as whether the bulk drug substance is poorly characterized or difficult to characterize

No bioburden/endotoxin test is mentioned in the CoA provided by the nominator. Endotoxin testing is considered a critical quality attribute to control microbiological quality of a BDS intended for an injection product. No such relevant information for Ta1 acetate was identified in the public domain. In addition, there is no residual solvent testing in the nomination.

Conclusions: Ta1 acetate is an acetate salt of the Ta1 (free base) peptide of 28 amino acids. As reported in the literature, Ta1 acetate is expected to be stable under storage conditions below -20°C. However, the stability of peptides, such as Ta1 acetate, is highly sensitive to the manufacturing process and quality attributes of the compounded or finished drug product.

Ta1 acetate is not well-characterized from the physical and chemical characterization perspective because certain critical characterization data specific to Ta1 acetate, including impurities, aggregates, bioburden, and bacterial endotoxins, were not found in publicly available scientific literature and the nomination package lacked information to establish identity, purity, and impurity profiles of the substance, such as specific tests in COAs. As discussed in Section II.C.2.d., FDA is concerned about the potential for immunogenicity of Ta1 acetate when formulated in an injectable dosage form for SC administration due to the potential for aggregation as well as potential peptide-related impurities, as discussed in Section II.A.1.c. Injectable routes of administration may present a particular risk for immunogenicity.

[21] https://lktlabs.com/product/thymosin-%CE%B1-1-acetate/. Accessed 10/31/24.

In addition, due to limited water solubility of Ta1 acetate, it is unclear how it would be possible to formulate the proposed injectable dosage form with a concentration of 3 mg/mL, and no information was provided to explain how this solubility could be achieved.

B. Has the substance been used historically in compounding?

This evaluation focuses on Ta1 (free base) and Ta1 acetate for SC injection and their use in treating hepatitis B, hepatitis C, HIV, COVID-19, depressed response to vaccinations; adjuvant to flu vaccines, malignant melanoma, HCC, NSCLC, sepsis, infections after HSCT, COPD, and ME/CFS; FDA searched generally for information on the historical use of Ta1 (free base) and Ta1 acetate in compounding. The information FDA found about use may not specify specific attributes of the product, such as the route of administration. Databases searched for information on both substances for this evaluation included PubMed, Google/Google Scholar, Micromedex, Clinical Pharmacology, NatMedPro Database, USP-NF, European Pharmacopoeia, Japanese Pharmacopoeia, European Medicines Agency, GlobalEdge.com, and the Outsourcing Facility Product Reporting Database.[22] It is often unclear whether the Ta1 discussed in the information from these sources is the free base or the salt form. Therefore, FDA will consider the information discussed in this section in its evaluation of both the free base and salt form as appropriate.

1. Length of time the substance has been used in compounding

The withdrawn nomination did not include historical use data.

Literature shows that Ta1 was isolated from calf thymus in 1977 (Goldstein et al. 1977). Starting in 1980, the National Cancer Institute initiated several phase 1 and phase 2 clinical trials with Ta1 at five institutions as part of their Biological Response Modifier program, a program within the Division of Cancer Treatment (Low and Goldstein 1984; Schulof et al. 1985; Smalley et al. 1984).

The earliest date and extent of Ta1 (free base) or Ta1 acetate use in compounding is unknown. A search of published literature did not yield results that specified the use of compounded formulations of Ta1 (free base) or Ta1 acetate in humans. However, according to a Form 483[23] issued in 2018, a 503A compounding pharmacy was compounding drug products containing Ta1, but the form of Ta1 used is unclear.[24]

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[22] Available at https://dps.fda.gov/outsourcingfacility. Accessed 6/5/24.

[23] An FDA Form 483 is issued to firm management at the conclusion of an inspection when an investigator(s) has observed any conditions that in their judgment may constitute violations of the FD&C Act and related Acts. Observations are made when in the investigator's judgment, conditions or practices observed would indicate that any food, drug, device or cosmetic has been adulterated or is being prepared, packed, or held under conditions whereby it may become adulterated or rendered injurious to health. For more information on FDA Form 483, please refer to *FDA Form 483 Frequently Asked Questions*, available at https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/fda-form-483-frequently-asked-questions

[24] https://www.fda.gov/media/135387/download.

According to outsourcing facility (OF) reports submitted to FDA between 2017 and the first half of 2024, OFs have not reported compounding any drug products containing Ta1 (free base) or Ta1 acetate.[25]

2. The medical condition(s) it has been used to treat

According to Micromedex, Ta1 has been used alone or with interferon as an immunomodulator for the treatment of chronic hepatitis B (CHB), chronic hepatitis C (CHC), chemotherapy-induced immunosuppression, to enhance the efficacy of influenza vaccines in immunocompromised or elderly patients, to enhance the efficacy of influenza and hepatitis B vaccines in chronic hemodialysis patients, and is "under investigation for hepatitis D, HIV infections, and AIDS."[26]

Results from a Google search using the terms "*Thymosin alpha-1 compounding*, *Thymosin alpha-1 acetate compounding*, *Ta1 compounding*, *Thymosin alpha-1 503A compounding pharmacy*, *Thymosin alpha-1 acetate 503A compounding pharmacy*, or *Thymalfasin compounding*" indicate that Ta1 is marketed online.

Ta1 is marketed on U.S. websites as follows:

- Modulates immunity to improve recovery time from viral infections such as SARS, HIV, hepatitis B, hepatitis C[27]
- Has antibacterial, anti-viral, and anti-fungal properties; enhances cellular immunity, helps to eradicate unhealthy cells; stops cancer growth; increases vaccine effectiveness; suppresses tumor growth; improves symptoms associated with chronic fatigue [28]
- Improves macrophages and B cells; balances T helper type 1 (Th1)/T helper type 2 (Th2) cells[29]
- Improves overall wellness, improves inflammation associated with arthritis and joint paint; is used for the treatment of asthma, eczema, Lyme disease, allergies, inflammatory bowel disease, and COPD[30]
- Use for COVID-19[31]

[25] The Drug Quality and Security Act, signed into law on November 27, 2013, created a new section 503B in the Federal Food, Drug, and Cosmetic Act. Under section 503B, a compounder can become an outsourcing facility. Outsourcing facilities are required to provide FDA with a list of drugs they compounded during the previous six month period upon initial registration and in June and December each year. This retrospective information does not identify drugs that outsourcing facilities intend to produce in the future.

[26] Thymalfasin (Martindale). https://www.micromedexsolutions.com/micromedex2/librarian/CS/C09775/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/CCF50C/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.IntermediateToDocumentLink?docId=1233-c&contentSetId=30&title=Thymalfasin&servicesTitle=Thymalfasin. Accessed 6/5/24.

[27] Help Patients Stay Health with Quad Immune. https://quadimmune.wellsrx.com/. Accessed 6/5/24.

[28] Thymosin Alpha-1: Patient Education. https://xsculpt.com/wp-content/uploads/2020/12/Thymosin_alpha_1.pdf. Accessed 6/5/24.

[29] Anti-Aging Peptide Therapy. https://vitasanacenter.com/aesthetic-medicine-peptide-therapy/. Accessed 6/5/24.

[30] Thymosin Alpha 1 in Santa Barbara, CA. https://www.amisantabarbara.com/thymosin-alpha-1. Accessed 6/5/24.

[31] Coronavirus: Thymosin Alpha-1 Peptide Therapy. https://www.jmisko.com/Ta1. Accessed 6/5/24.

- Used for "long COVID"; chronic Lyme disease; chronic mononucleosis; chronic fatigue syndrome; parasitic infections[32]
- Protects against oxidative stress[33]
- Enhances the function of immune cells (T cells and dendritic cells)[34]
- Curbs morbidity and mortality in sepsis[35]
- Acts as adjunct to cancer therapy, acts as an antioxidant[36]
- Used in Chronic Inflammatory Response Syndrome (CIRS) due to toxic mold, multiple sclerosis; psoriatic arthritis; acute respiratory viral infections and lung infections; and increases sperm function[37]

A United Kingdom (UK) wellness clinic markets Ta1 for its anti-inflammatory, anti-viral, and anti-cancer properties. It states that Ta1 has neuroprotective effects, strengthens the immune system, lowers the risk of infection, and acts as "a powerful immunomodulator."[38] Another UK clinic states that "Studies have postulated that thymosin alpha 1 could help improve the outcome in severely ill coronavirus patients by repairing damage caused by overactivation of lymphocytic immunity and how thymosin alpha 1 could prevent the excessive activation of T cells."[39]

3. How widespread its use has been

Results from an internet search for compounded drug products containing Ta1 revealed that it is compounded as an injection and as a nasal spray in the U.S. A naturopathic medical clinic, holistic wellness center, and intravenous (IV) hydration lounge market compounded drug products containing Ta1 as 3 mg and 10 mg nasal sprays.[40] A compounded 5 mL solution of Ta1 with a strength of 3 mg/mL for SC administration is marketed as part of a "Quad Immune" package; this package also contains oral zinc picolinate, oral vitamin D_3, and injectable vitamin B complex with vitamin C, and is sold as a combination of four different products.[41] A concierge aesthetics website advertises a 3 mg/mL (5 mL vial) Ta1 product for SC injection that is "FDA approved"; however FDA has approved no drug products containing Ta1. Further, the website states that the drug product is compounded specifically by 503A compounding pharmacies.[42]

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[32] Peptide Therapy: Thymosin and BPC-157. https://wholehealthchicago.com/blog/2023/03/06/peptide-therapy-thymosin-and-bpc-157. Accessed 6/5/24.
[33] Peptide Therapies for Optimal Health. https://lamkinclinic.com/growth-hormone-and-peptide-therapies/. Accessed 6/5/24.
[34] "Thymosine Alpha-1" https://www.iwholehealth.com/peptide-therapy/thymosine-alpha-1/. Accessed 6/5/24.
[35] Peptide Therapy in Boca Raton, FL. https://www.amtcare.com/treatments/peptide-therapy.html. Accessed 6/5/24.
[36] Thymosin Alpha 1 Peptide 15mg. https://drjennpb.com/product/thymosin-alpha-1-peptide-15mg/. Accessed 6/5/24.
[37] Peptide Therapy to Balance Immune Function. https://www.drlaurendeville.com/peptide-therapy/. Accessed 6/5/24.
[38] Thymosin-Alpha 1 Peptide: A Powerful Immunomodulator with Wide-Ranging Benefits. https://nuutro.co.uk/the-science/peptide-therapy/thymosin-alpha-1-peptide-a-powerful-immunomodulator-with-wide-ranging-benefits/. Accessed 6/5/24.
[39] Peptide Protocol: Thymosin Alpha-1. https://www.healand.co.uk/peptideprotocolthymosinalpha1. Accessed 6/5/24.
[40] Thymosin Alpha. https://livvnatural.com/product/thymosin-alpha/# and https://livvnatural.com/product/thymosin-alpha-10mg/. Accessed 6/5/24.
[41] Help Patients Stay Healthy with Quad Immune. https://quadimmune.wellsrx.com/. Accessed 6/5/24.
[42] Thymosin Alpha 1 Peptide 15mg. https://drjennpb.com/product/thymosin-alpha-1-peptide-15mg/. Accessed 6/5/24.

Telemedicine, wellness clinics, and concierge service websites also assert that they work with compounding pharmacies to obtain compounded peptide drug products containing Ta1.[43]

OFs have not reported compounding drug products containing Ta1 (free base) and Ta1 acetate from 2017 to the first half of 2024.

4. Recognition of the substance in other countries or foreign pharmacopeias

A search of the European Pharmacopoeia (11th Edition - 11.5) and the Japanese Pharmacopoeia (18th Edition) did not show any monograph listings for Ta1 or Ta1 acetate. The European Medicines Agency (EMA) database indicates that Ta1 was granted orphan designation[44] for the treatment of HCC.[45]

According to the 2014 annual report of SciClone Pharmaceuticals,[46] Ta1 is approved for use in countries in the Asia-Pacific region, Latin America, Eastern Europe, and the Middle East regions. These approvals are primarily for the treatment of hepatitis B virus (HBV) infection and as a vaccine adjuvant, with additional approvals in certain countries for the treatment of hepatitis C virus (HCV) infection, or as a chemotherapy adjuvant for cancer patients with weakened immune systems.[47] Specifically, Ta1 is approved in Italy as an adjuvant to the influenza vaccine in immunocompromised subjects.[48] It is approved in India as an injection for the treatment of CHB in patients 18 years or older with compensated liver diseases and HBV replication.[49] Ta1 is also approved in Hong Kong.[50]

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[43] What is Peptide Therapy? https://www.iwholehealth.com/peptide-therapy/, Peptide Therapy https://www.hawaiiwholepersonhealing.com/peptides/, What is Peptide Therapy? https://www.transformyou.com/peptide-therapy, Peptides and Immunity: What is Thymosin Alpha-1? https://dramybrenner.com/peptides-and-immunity-what-is-thymosin-alpha-1/. Accessed 6/5/24.

[44] The European Medicines Agency (EMA) orphan designation is granted to substances that can be used for treating, preventing, or diagnosing a rare and serious condition. Orphan designation can help the medicine's developer advance the medicine to the stage where it can be authorized to be put on the market. Under the European Commission, formal approval is considered marketing authorization. It is needed before a medication can legally be marketed. Orphan designation itself does not permit the use of a medicine and does not indicate formal approval. For more information regarding the EMA's orphan designation, see https://www.ema.europa.eu/en/human-regulatory-overview/orphan-designation-overview, https://www.ema.europa.eu/en/documents/other/rare-diseases-orphan-medicines-getting-facts-straight_en.pdf, and https://www.ema.europa.eu/en/human-regulatory-overview/orphan-designation-overview/legal-framework-orphan-designation.

[45] EU/3/02/110 - orphan designation for treatment of hepatocellular carcinoma. https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu302110. Accessed 6/20/24.

[46] 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. It is unclear whether SciClone Pharmaceuticals remains in business. FDA is unable to independently verify these claims of approval in the specified countries.

[47] SciClone Pharmaceuticals – 2014 Annual Report. https://www.annualreports.com/HostedData/AnnualReportArchive/s/NASDAQ_SCLN_2014.pdf. Accessed 7/25/24.

[48] Zadaxin. https://medicinali.aifa.gov.it/it/#/it/dettaglio/0000022315. Accessed 6/20/24.

[49] Drugs@CDSCO: Thymosin alfa-1 inj. https://cdscoonline.gov.in/CDSCO/Drugs. Accessed 6/20/24.

[50] Zadaxin for Inj. 1.6 mg. https://www.drugoffice.gov.hk/eps/drug/productDetail2/en/consumer/152754. Accessed 6/20/24.

A Ta1 monograph from Singapore states that Ta1 injection is indicated for use in chronic hepatitis B and C.[51] A Ta1 monograph from Mexico states that Ta1 is indicated for monotherapy or therapy with interferon (IFN) alfa 2b in the treatment of chronic hepatitis B in patients over 18 years of age with compensated liver disease and proven viral replication and as an adjuvant to anti-influenza vaccination in immunocompromised subjects.[52]

Conclusions: It is often unclear whether the Ta1 discussed in the sources considered for this section are the salt form or the free base. Available literature indicates that Ta1 was discovered by researchers in 1977. A search of published literature did not reveal studies in which compounded drug products containing Ta1 (free base) or Ta1 acetate were used in humans, and OFs have not reported preparing compounded drug products containing Ta1 or Ta1 acetate. However, results from internet searches for compounded drug products containing Ta1 revealed that it is being compounded as an injection and as a nasal spray. Compounded Ta1 is marketed for use in conditions such as hepatitis B, hepatitis C, HIV, chronic fatigue, inflammation, sepsis, COVID-19, Lyme disease, allergies, cancer, asthma, COPD, and psoriatic arthritis, but the length of time that these products have been marketed is unclear. Ta1 is licensed and marketed in many countries. Ta1 is not recognized in the European or Japanese Pharmacopoeias.

C. Are there concerns about the safety of the substance for use in compounding?

1. Nonclinical Assessment

The nomination included nonclinical information in the form of two review articles that discuss the pharmacological properties of Ta1 (Chien and Liaw 2004; Tuthill and King 2013).

The following databases were consulted in preparation of this section: Drugs@FDA, Embase, European Chemicals Agency, FDA's Generally Recognized as Safe (GRAS) Notice Inventory, Google, Google Scholar, National Institutes of Health's dietary supplement label database, National Toxicology Program website, Pharmapendium, PubMed, Society of Toxicology, USP, and Web of Science.

The nonclinical articles included in the nomination and those identified by FDA do not always clearly identify Ta1 as free base or salt. Therefore, in this section, the substance is referred to as Ta1, unless an article specifies the use of Ta1 (free base) or Ta1 acetate.

a. General pharmacology of the drug substance

Thymosin alpha-1, the active moiety of Ta1 (free base) and Ta1 acetate, is an N-acetylated 28-amino acid peptide that was originally isolated from an immunologically active fraction of bovine thymus extract (Low et al. 1979; Low and Goldstein 1979). Following determination of its amino acid sequence, Ta1 became available as a synthetic peptide (Wang et al. 1979). Figure 5 illustrates the amino acid sequence of Ta1.

[51] Zadaxin Injection. https://www.ndf.gov.sg/monograph/Detail/M00600. Accessed 6/20/24.
[52] Timalfasina (L03AX M4). https://www.vademecum.es/principios-activos-timalfasina-l03ax+m4-es. Accessed 6/24/24.

Figure 5. Amino Acid Sequence of Ta1 (Adapted from Low and Goldstein 1979).

Left to right: Amino acid sequence from the N- to the C-terminus of Ta-1. Ala: alanine; Asn: asparagine; Asp: aspartic acid; Glu: glutamic acid; Ile: isoleucine; Leu: leucine; Lys: lysine; Ser: serine; Thr: threonine; Val: valine. All are L amino acids. Ac represents the acetate modification of the N-terminal domain.

Low and Goldstein reported that synthetic and native Ta1 have similar immunomodulatory properties in the in-vitro lymphokine assay, which measures the production of macrophage inhibitor factor by human lymphocytes, and in the in-vitro human E-rosette assay, which measures the generation of CD2 (also referred to as E rosette receptor)-expressing T cells (Low and Goldstein 1979).

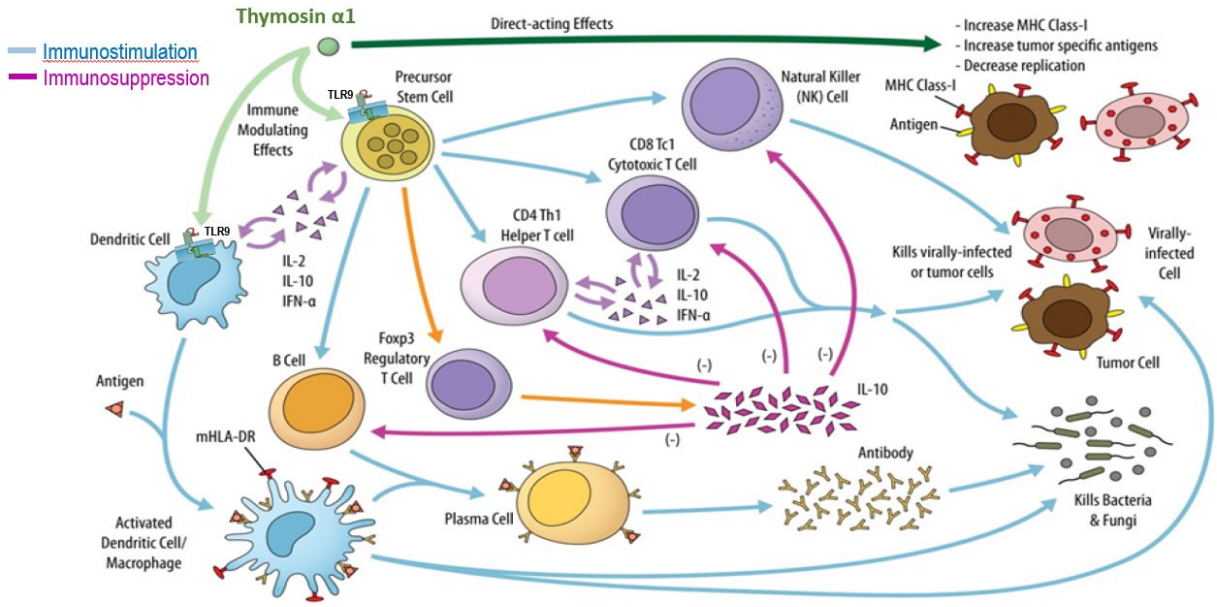
As discussed in the review by Tuthill and King (2013), several in-vitro and in-vivo pharmacological studies have reported that Ta1 acts as an immunostimulant. Specifically, it has been reported that:

- Ta1 can increase the activity of natural killer (NK) cells, which are effector lymphocytes of the innate immune system that limit the spread of tumors and microbial infections, thereby suppressing the associated tissue damage.
- Ta1 can shift CD4+ T helper cells from the Th2 to the Th1 phenotype. Th1 CD4+ cells are known to produce cytokines such as interferon gamma (IFN-γ) and interleukin-2 (IL-2) that are key to intracellular defense against microorganisms.
- Ta1 can increase the expression of Th1-related cytokines, including IL-2 and IFN-γ.
- Ta1 can increase the numbers of cytotoxic CD8+ T cells, also known as Tc1 cells, which can produce and release cytolytic cytokines such as IFN-γ, granzyme B, and tumor necrotic factor (TNF)-α.
- Ta1 can increase activation of dendritic cells, which are known to capture, process, and present antigens to lymphocytes to initiate and regulate the adaptive immune response.

Because the studies cited by Tuthill and King (2013) list Ta1 as the test substance and do not provide a test article catalog number or the source, it is unclear whether Ta1 in those studies was the free base or the acetate salt, which may have distinct pharmacokinetic properties. However, the pharmacological properties of the active moiety, Ta1, which are the focus of this section, will define the pharmacological effects of Ta1 (free base) and Ta1 acetate.

As illustrated in Figure 6, the immunostimulant effects of Ta1 are proposed to be mediated at least in part by its interactions with toll-like receptor 9 (TLR9) on dendritic cells and on lymphoid progenitor cells (Tuthill and King 2013). In dendritic cells, Ta1-induced TLR stimulation can lead to their activation and initiation of antigen-specific immune responses. In lymphoid progenitor cells, Ta1-induced TLR stimulation can induce their differentiation into B cells and different types of T cells, which mount the immune response that help fight infections and tumors (Tuthill and King 2013).

Figure 6. Mechanisms Underlying the Immunostimulatory and Immunosuppressive Effects of Ta1 (Adapted from Tuthill and King 2013).



Abbreviations: IL = interleukin; IFN = interferon; MHC = major histocompatibility antigen; mHLA = monocyte human lymphocyte antigen; NK = natural killer; Tc1 = cytotoxic Th1-like cell subset of T cells; Th1 = T helper 1 subset of T cells; TLR = toll-like receptor

Via TLR-independent mechanisms, which are poorly understood, Ta1 can also directly act on cancer cells or infected cells to increase surface expression of antigen-specific receptors, including major histocompatibility (MHC) class I proteins, thereby enhancing the ability of the immune system to recognize and target those cells (Garaci et al. 2012; Giuliani et al. 2000).

It has been proposed that, due to its ability to enhance the activity of indoleamine-2,3-dioxygenase (IDO) in dendritic cells, Ta1 may self-regulate its effects by activating a feedback inhibitory mechanism that prevents the development of a proinflammatory cytokine storm (Romani et al. 2006). IDO is the first enzyme in the catabolic pathway that converts tryptophan into kynurenines. The immunosuppressive activity of IDO has been suggested to be due to: (i) starvation of T cells or other effector cells due to the depletion of the essential amino acid tryptophan, and/or (ii) direct actions of kynurenines on CD4+ T cells and other T cells. This leads to the expansion of Foxp3+ T-regulatory cells, which can release anti-inflammatory cytokines (particularly IL-10) that, in turn, suppress the activity of CD4+ T cells, Tc1 cells, NK cells, and B cells (Tuthill and King 2013).

According to nonclinical pharmacological studies, Ta1, acting as an immunomodulator, suppressed cancer growth, sepsis, and viral infections in in-vivo and in-vitro models. For instance, treatment of a murine model of lung cancer with Ta1 (10 mg/kg, SC, twice a day [BID]) compared to vehicle (phosphate buffered saline) for 7 days significantly suppressed tumor growth (King and Tuthill 2015). Likewise, in mice inoculated with B16F10 melanoma cells, treatment with Ta1 (free base, 0.02, 0.05, 0.2, 0.6, 2.0 or 6 mg/kg, SC, BID) compared to vehicle (phosphate buffered saline) for 7 days starting after the tumors had reached ~120 mm^3 also suppressed tumor growth (King and Tuthill 2015). However, the effect was not dose dependent, as all tested doses reduced tumor size by 45-50% (King and Tuthill 2015).

Considering their findings that plasma concentrations of the proinflammatory cytokine IL-1β were significantly lower in melanoma-inoculated mice following treatment with Ta1 compared to vehicle, the authors concluded that the immunomodulatory properties of Ta1 contributed to its antitumorigenic effects in this model (King and Tuthill 2015). We note, however, that the Ta1-induced reduction of melanoma tumor growth in mice was not dose dependent, whereas Ta1-induced reduction of IL-1β levels was. Therefore, the relationship between the two pharmacological effects is unclear.

In a murine model of sepsis induced by cecal ligation and puncture, there was a trend toward reduced bacterial load in Ta1 (6 mg/kg, SC, BID)-treated compared to saline-treated mice. There was also a trend towards prolonged life at 7 days post-sepsis induction in Ta1-treated compared to saline-treated mice. However, the effects did not reach statistical significance (King and Tuthill 2015).

In murine models of cytomegalovirus infection, Ta1 (reconstituted in sterile water; 200 µg/kg/day) compared with vehicle (sterile water) delivered through the intraperitoneal (IP) route for 7 or 14 days starting on postinfection day 1 significantly decreased the viral loads in visceral organs (Bozza et al. 2007). The authors proposed that the anti-viral effect of Ta1 was mediated by activation of dendritic cells via the TLR9/myeloid differentiation primary response gene 88 (MyD88)-dependent viral recognition sensor, leading to the activation of IFN regulatory factor 7 (IRF7) and stimulation of the IFN-α/IFN-γ-dependent effector pathway (Bozza et al. 2007).

In an in-vitro study, 48-hour incubation of LPS-stimulated CD8+ T cells with Ta1 (100 µg/mL) increased the release of soluble factors that inhibited in-vitro infection of human monocyte-derived macrophages and peripheral blood mononuclear cells (PBMCs) with HIV-1 (Matteucci et al. 2015). These findings suggested that Ta1 has potential to suppress HIV infections. However, the concentration of Ta1 was nearly 2,000 times higher than the maximal plasma levels generated by the SC dose of Ta1 used in most clinical studies (1.6 mg) (Rost et al. 1999).

Nonclinical pharmacological studies have also reported that, in mice, antibody titers generated by some vaccines could be increased by post-vaccination treatment with Ta-1 (see Tuthill and King 2013 and references therein). For instance, in a study by Ershler et al., young adult (2- to 3-month-old) and old (23-month-old) C57Bl/6 mice received a SC injection of a tetanus vaccine (0.5 µg/mouse) and were subsequently treated with daily IP injections of Ta1 (free base; 0.05 or 0.5 µg/kg) or vehicle for 4 consecutive days starting on the day of the vaccine injection (Ershler et al. 1985). The authors reported that between 10 and 36 days after the vaccine injection, mice developed a time-dependent increase in plasma anti-tetanus toxoid antibodies. The antibody titers were approximately 25-35% higher in young mice treated with Ta1 than in vehicle-treated, age-matched mice. A similar result was obtained from old mice treated with the higher dose of Ta1 (0.5 µg/kg, SC) (Ershler et al. 1985). By contrast, results from similar experiments in which mice received the Pneumovax vaccine indicated that posttreatment with Ta1 did not increase titers of anti-Pneumovax antibodies (Ershler et al. 1985). The authors suggested that the discrepant findings reflected the T-cell independence for antibody response to polysaccharide-like antigens such as Pneumovax (Ershler et al. 1985). We note that Ta1 is a substance with pleiotropic immunomodulating properties, and we cannot rule out the possibility of undesirable

interference with vaccine immune responses should Ta1 be administered together with a vaccine as an adjuvant.[53]

In summary, nonclinical in-vitro and in-vivo studies have reported that Ta1 suppressed tumor growth, suppressed viral infections, and decreased sepsis. There are also nonclinical reports that, as a posttreatment, Ta1 increased antibody titers generated by some vaccines in mice. However, as described earlier[53] and further discussed in section II.D.5, should Ta-1 be used as a vaccine adjuvant, the vaccine product (including the vaccine adjuvant) would need to be evaluated in the context of a specific vaccine. We also note that there is lack of clarity regarding the Ta1-related substance (e.g., Ta1 (free base), Ta1 acetate) tested in most studies, and the doses of the Ta1-related substances and the ROAs are inconsistent across the studies. In addition, most nonclinical pharmacological studies used fixed doses of Ta1-related substances that, according to the body surface area (BSA), translate to human equivalent doses markedly higher than the SC doses of Ta1 used in most clinical studies (1.6 mg; see section II.D). For instance, according to BSA, the SC dose of 10 mg/kg of Ta1 that suppressed the growth of lung tumor cells in mice and the SC dose of 6 mg/kg of Ta1 that tended to suppress the bacterial load in a mouse model of sepsis (King and Tuthill 2015) translate to human equivalent doses of approximately 49 mg and 29 mg, respectively. Due to a lack of well-defined dose-response relationships, it is difficult to determine the minimal Ta1 dose required to induce a pharmacological response. Also, due to the lack of assessments of systemic Ta1 exposures in the nonclinical studies, the minimal systemic exposure required to induce a pharmacological effect is unknown. Therefore, it is difficult to define the clinical relevance of the pharmacological findings discussed above.

b. Pharmacokinetics/Toxicokinetics (TK)

Two studies assessed the PK profile of Ta1 delivered via the IV ROA to rats. One study was conducted in Wistar rats (Wang et al. 2018) and the other in Sprague-Dawley rats (Shen et al. 2019). Although the IV dose of Ta1 was approximately 0.175 mg/kg in both studies, the systemic exposures and the half-lives ($t_{1/2}$) of Ta1 differed between the studies (Table 3).

Table 3. PK Profile of Ta1 (0.175 mg/kg, IV) in Wistar and Sprague-Dawley Rats.

	Wistar Rats[1]	Sprague-Dawley Rats[2]
C_{max} (ng/L)	70	20.5
$AUC_{0-\infty}$ (ng/L•h)	191	120
$t_{1/2}$ (hours)	1.9	3.0

[1]Ta1 concentrations were quantified in serum, the liquid phase from coagulated blood (Wang et al. 2018). [2]Ta1 concentrations were quantified in plasma, the liquid phase from anticoagulant-treated blood (Shen et al. 2019). C_{max} = maximal concentration; $AUC_{0-\infty}$ = area-under-the-curve of the concentration-vs-time plot; $t_{1/2}$: half-life.

[53] As discussed in section II.D.5, per the FDA webpage *Common Ingredients in FDA-Approved Vaccines*, available at https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/common-ingredients-fda-approved-vaccines#:~:text=An%20adjuvant%20is%20a%20substance,)%2C%20or%20mixed%20aluminum%20salts, a vaccine adjuvant is "a substance added to some vaccines to enhance the immune response of vaccinated individuals." When evaluating a vaccine for safety and effectiveness, FDA considers an adjuvant to be a component of a vaccine, and adjuvants are not approved separately. Further information about nonclinical evaluation of vaccine adjuvants can be found in the *Guidelines of the Nonclinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines,* available at https://www.who.int/publications/m/item/nonclinical-evaluation-of-vaccine-adjuvants-and-adjuvanted-vaccines-annex-2-trs-no-987.

The following could help explain the discrepant findings between the two studies: (i) Ta1 disposition may be different between the two rat strains, and/or (ii) in part due to protein binding, the concentrations of Ta1 may differ between serum (assayed in the study by Wang and colleagues) and plasma (assayed in the study by Shen and colleagues).

In female Swiss Webster mice treated via the IP ROA with Ta1 (reconstituted in phosphate-buffered saline to 1 mg/mL; dose: 500 µg/mouse), serum concentrations of Ta1 were above baseline by approximately 2 minutes, peaked at 1.9 µg/mL by 20 minutes, and declined to baseline by 5 hours posttreatment (Badamchian et al. 1997). Ta1 distributed to different organs, as its concentrations increased time dependently in the thymus, lungs, spleen, kidneys, ovaries, and peritoneal fat. Ta1 concentrations did not increase in the liver, heart, brain, or skeletal muscles of Ta1-treated mice (Badamchian et al. 1997).

Following the IP treatment of female mice, the main route of elimination of Ta1 was urine. At 24 hours after dosing, approximately 40% of the administered dose of Ta1 was recovered in urine (Badamchian et al. 1997).

The nomination did not include, and, at the time of this evaluation, FDA has not identified nonclinical PK or TK studies of Ta1 (free base) or Ta1 acetate delivered via the nominated SC ROA.

c. Acute toxicity[54]

According to a product monograph from SciClone Pharmaceuticals, the maker of the internationally marketed Ta1 (free base)-containing drug product Zadaxin, SC doses of Ta1 (free base) up to 20 mg/kg generated no drug-related safety signals in single-dose toxicity studies in mice, rats, and marmosets (SciClone Pharmaceuticals 2024). Using the BSA to translate the animal doses into human doses, the single SC dose of 20 mg/kg in mice, rats, and marmosets provides safety margins of approximately 61-fold, 121-fold, and 243-fold to the human SC dose of 1.6 mg (which corresponds to approximately 0.027 mg/kg for a 60-kg adult) commonly used in clinical studies.

FDA notes that the Zadaxin monograph does not provide the nonclinical acute toxicity data from which the conclusion was drawn. In addition, the nomination did not include, and FDA has not identified in the published literature nonclinical acute toxicity studies of Ta1 (free base) or Ta1 acetate.

[54] Acute toxicity refers to adverse effects observed following administration of a single dose of a substance, or multiple doses given within a short period (approximately 24 hours). For more information on general approaches for acute toxicity studies, please refer to FDA's guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010), available at https://www.fda.gov/media/71542/download.

d. Repeat-dose toxicity[55]

According to the Zadaxin monograph, treatment of mice, rats, and marmosets with Ta1 SC doses of up to 6 mg/kg/day administered up to 13 weeks or with Ta1 SC doses of up to 1 mg/kg/day administered up to 26 weeks generated no drug-related safety signals (SciClone Pharmaceuticals 2024).

Using the BSA to translate the animal doses into human doses, the SC dose of 1 mg/kg in mice, rats, and marmosets provides safety margins of approximately 3-fold, 6-fold, and 12-fold to the daily human SC dose of 1.6 mg.

FDA notes that the monograph does not provide the nonclinical repeat-dose toxicity data from which the conclusion was drawn. In addition, the nomination did not include, and FDA has not identified in the published literature nonclinical repeat-dose toxicity studies of Ta1 (free base) or Ta1 acetate.

e. Genotoxicity[56]

According to the Zadaxin monograph, Ta1 did not produce safety signals in in-vivo and in-vitro genotoxicity assays (SciClone Pharmaceuticals 2024). The monograph does not describe which assays were conducted to assess the genotoxicity potential of Ta1 and does not provide data from which the safety conclusion was drawn.

The nomination did not include, and, at the time of this evaluation, FDA has not identified in the published literature nonclinical genotoxicity studies of Ta1 (free base) or Ta1 acetate.

f. Developmental and reproductive toxicity[57]

In an in-vitro study, 5-to-6-hour incubation of human sperm cells with Ta1 (0.1 to 100 µg/mL) increased their fertilization capacity, as measured by the percentage of unfertilized hamster ova

[55] Repeat-dose toxicity studies consist of in-vivo animal studies that seek to evaluate the toxicity of the test substance when it is repetitively administered daily for an extended period. For more information on general approaches for repeat-dose toxicity studies, please refer to FDA's guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010), available at https://www.fda.gov/media/71542/download.

[56] The genotoxicity assessment battery usually consists of a gene mutagenicity assay (for single dose trials) and a variety of clastogenicity/genotoxicity assays. To support multiple dose administration in humans, additional genotoxicity testing assessment is usually conducted to detect chromosomal damage in mammalian systems. For more information on general approaches for genotoxicity studies, please refer to FDA's guidance for industry *S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use* (June 2012), available at https://www.fda.gov/media/71980/download.

[57] Developmental and reproductive toxicity studies are usually designed to assess the potential adverse effects of a substance within a complete reproductive cycle, from conception to reproductive capacity in subsequent generations, and to identify the potential effects of a substance on pre-, peri-, and postnatal development. Developmental toxicity or teratogenicity refers to adverse effects (can include embryo-fetal mortality, structural abnormalities, functional impairment, or alterations to growth) and can occur in pups either as a result of the exposure of their parents to the substance, prior to the pups' birth, or by direct exposure of the pups to the substance after birth. For more information on general approaches for reproductive and developmental toxicity studies, please refer to FDA's

that were penetrated by the sperm in vitro (Naz et al. 1992). The concentration-response relationship for the effect of Ta1 on sperm fertilization capacity was bell shaped, with the effect peaking at 5 µg/mL and decreasing in magnitude as the concentration of Ta1 increased from 5 µg/mL to 100 µg/mL (Naz et al. 1992).

According to a review article, SciClone Pharmaceuticals "successfully completed" a "lengthy Segment 3 Reproductive Toxicology" study (Tuthill 2007), which is a perinatal and postnatal developmental study in rodents with the purpose of assessing the effects of a test article during the last third of gestation and the period of lactation (Colerangle 2017). The author of the review provides no details on the Ta1 study, does not report the study outcomes, and does not provide a reference to support the statement.

The nomination did not include, and, at the time of this evaluation, FDA has not identified in the published literature nonclinical developmental and reproductive toxicity studies of Ta1 (free base) or Ta1 acetate.

g. Carcinogenicity[58]

The nomination did not include, and, at the time of this evaluation, FDA has not identified in the published literature nonclinical carcinogenicity studies of Ta1 (free base) or Ta1 acetate.

Conclusions: From the nonclinical pharmacological perspective, Ta1 – the active moiety of Ta1 (free base) and Ta1 acetate – has immunomodulatory properties attributable to Ta1-induced activation of TLRs on dendritic cells and lymphoid progenitor cells. The immunomodulatory properties of Ta1 are thought to contribute to its ability to suppress cancer growth, sepsis, and viral infections in nonclinical in-vivo and in-vitro models. However, it is difficult to define the clinical relevance of the nonclinical pharmacological findings in part because: (i) the doses and ROAs of Ta1 are inconsistent across the studies, and (ii) most studies used fixed Ta1 doses that, according to BSA, translate to human equivalent doses markedly higher than the SC doses of Ta1 commonly used in clinical studies. In addition, concentrations of Ta1 shown to induce CD8+ T cells to release soluble factors that blocked HIV infection of macrophages and PBMCs in vitro were 2,000 times higher than the maximal plasma concentrations generated by the Ta1 dose commonly used in clinical studies. From the nonclinical toxicological perspective, summaries of nonclinical toxicity studies available in a product monograph from SciClone Pharmaceuticals, the maker of the internationally marketed drug product Zadaxin that contains Ta1 (free base, 1.6 mg/mL), suggest that Ta1 (free base) did not induce safety signals in acute and repeat-dose toxicity studies and in genotoxicity studies. However, the nonclinical data from these studies are not included in the monograph. In addition, the nomination did not include, and, at the time of this evaluation, FDA has not identified published nonclinical toxicity studies of

guidance for industry *S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals* (May 2021), available at https://www.fda.gov/media/148475/download.

[58] Studies that assess cancer risk in animals are used as predictive tools to evaluate the potential for drugs to cause tumors when used by humans on a chronic basis. Carcinogenicity studies are conducted if the clinical use is expected to be continuous for a minimum of 6 months of life, or if intermittent clinical use is expected to total 6 months or more of life. For more information on general approaches for carcinogenicity studies, please refer to FDA's guidance for industry *S1B Testing for Carcinogenicity of Pharmaceuticals* (July 1997), available at https://www.fda.gov/media/71935/download.

Ta1(free base) or Ta1 acetate. Therefore, available nonclinical data are too limited to inform safety considerations for potential clinical uses of Ta1 (free base) and Ta1 acetate.

2. Human Safety

The following databases were consulted in the preparation of this section: PubMed, Embase, Cochrane Database of Systematic Reviews, FDA Adverse Event Reporting System (FAERS), the Center for Food Safety and Nutrition (CFSAN) Adverse Event Reporting System (CAERS), ClinicalTrials.gov, the websites of professional healthcare organizations, and various online clinical references and websites.

The clinical articles included in the nomination and those identified by FDA do not always clearly identify Ta1 as a free base or salt. Therefore, in this section, the substance will be generally referred to as Ta1, unless the article under discussion clearly specifies the use of the free base or the acetate salt in a study.

a. Pharmacokinetic data

The endogenous levels of serum Ta1 in healthy adults are 0.1-1 ng/mL. Ta1 concentrations are highest in the thymus, but Ta1 has also been detected in the spleen, lung, kidney, brain, blood, and several other tissues (Tuthill et al. 2000).

In this section, we include PK studies that measured Ta1 blood concentrations in humans after exogenous administration of Ta1. We identified two studies which are described below.

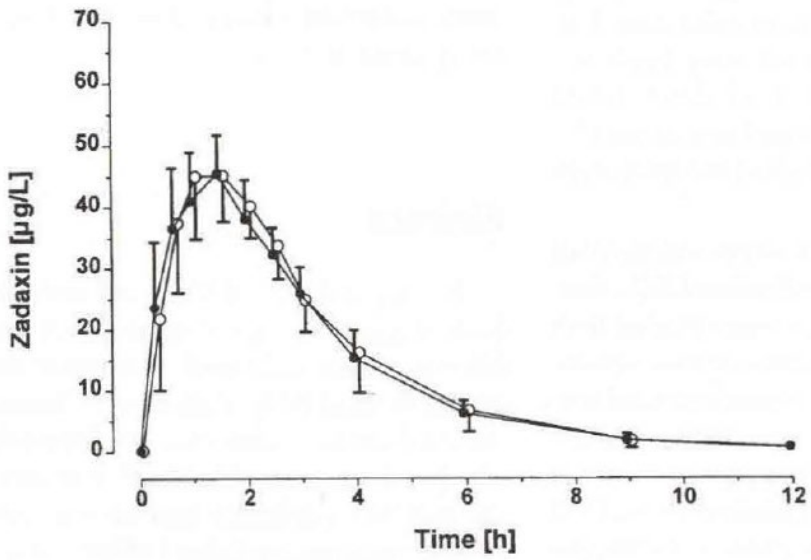
Schulof et al. (1984): Authors describe preliminary results from a randomized (R), double blind (DB), phase 2 study in 42 subjects with locally advanced NSCLC. The study was designed to compare the PK and immunorestorative effects of Ta1 administered SC on a twice a week (BIW) or a loading dose schedule. All subjects had locally advanced, unresectable, but not distally metastatic NSCLC. Subjects received radiation therapy over 6-8 weeks and then were randomized to one of three treatment groups: 1) Ta1 loading dose (900 $\mu g/m^2$ daily for 14 days) followed by twice weekly maintenance (900 $\mu g/m^2$) (n=13); 2) Ta1 900 $\mu g/m^2$ twice weekly (n=15); or 3) placebo twice weekly (n=13). Subjects continued treatment for up to 1 year or until relapse. Plasma Ta1 was measured by radioimmunoassay. Endogenous Ta1 plasma concentrations were reported to be around 1 ng/mL. After a single dose of Ta1, authors reported that plasma levels increased 10-fold 1 hour after administration and peak levels (C_{max}) were 25-30 ng/mL. Peak levels persisted for approximately 6 hours and then returned to near baseline over the next 18 hours. Baseline pre-dose plasma Ta1 levels, drawn just prior to Ta1 dosing, gradually increased from 1 ng/mL to up to 1.5 to 2 ng/mL over 15 weeks.

Rost et al. (1999): Authors conducted a R, single blind, balanced 3-way crossover study comparing three Ta1 products in 9 healthy subjects after single and repeat doses of Ta1. Subjects were randomized to receive: Zadaxin (Ta1 from **SciClone**; 1.6 mg/mL when reconstituted), Timosina (Ta1 from **Sclavo**; 2 mg/mL when reconstituted), and Ta1 from **Hoffman-La Roche** (Ta1-HLR; 2 mg/mL when reconstituted). Ta1 was administered as a 900 $\mu g/m^2$ SC injection on days 1, 3, 4, 5, 6, and 7 within each study period. Actual Ta1 doses ranged from 1.6 to 2.2 mg. Each of the three study periods comprised of 7 days and study periods were separated by a

washout phase of 5-8 days. Ta1 was measured in serum using ELISA with a limit of quantification (LOQ) of 0.1 µg/L (0.1 ng/mL). Endogenous serum concentrations were below the LOQ for most subjects.

After a single dose, Ta1 was rapidly absorbed from the injection site with T_{max} values ranging from 0.67-2 hours in all formulations. C_{max} values ranged from 32.6-78.9 µg/L with a preference for higher levels but also higher variability for Timosina. Except for two subjects with serum concentrations of 0.46 and 0.67 µg/L 24 hours after Timosina administration, all Ta1 concentrations declined to levels very close to or below the LOQ. Of note, the $AUC_{0\text{-}12h}$ and $AUC_{0\text{-}\infty}$ were significantly higher after Timosina compared with Zadaxin or Ta1-HLR. The elimination half-life was short (means of 1.8-2.6 hours). Figure 7 below is an example of a mean serum concentration vs time profile for Zadaxin.

Figure 7. Mean (± SD) Serum Concentrations of Ta1 After Single Dose (Filled Circles) and Multiple Dose (Open Circles) Administration of Zadaxin 900 µg/m^2 SC (Rost et al. 1999).



After daily dosing for five days, there was no evidence of accumulation, and the PK parameters resembled those calculated for a single dose. Authors concluded that a comparison of the three formulations indicate a moderate influence of drug formulation on systemic availability of Ta1.

In summary, after SC administration, Ta1 is absorbed rapidly with a T_{max} of approximately 2 hours and a serum half-life of approximately 2 hours. There is no evidence of accumulation following multiple doses using once daily dosing.

b. Reported adverse reactions (FAERS, CAERS, and case reports and anecdotal cases assessing safety)

The Office of Surveillance and Epidemiology conducted a search of the FAERS database for reports of adverse events (AEs) for Ta1 (thymosin and thymalfasin) in the U.S. through June 10, 2024.[59] The search retrieved one applicable report.[60]

A 46-year-old male with a history of chronic hepatitis C, palpitations of unknown etiology, tinnitus, and vertigo was receiving peginterferon alpha-2a 180 µg SC once per week and Ta1 1.6 mg SC twice weekly as part of a clinical trial. The patient had been receiving peginterferon alfa-2a and Ta1 for approximately 12 weeks. Three days after his most recent doses of peginterferon alfa-2a and Ta1, the patient was hospitalized with anxiety, atrial fibrillation, and a "transient decrease in his TSH [thyroid-stimulating hormone] levels." Treatment with both peginterferon alfa-2a and Ta1 was "interrupted," and he received atenolol, diltiazem, and heparin. He was discharged from the hospital the following day. Interpretation of causality in this case is confounded by concurrent use of peginterferon alfa-2a, because the three reported AEs are described in the U.S. labeling for peginterferon alfa-2a as potential AEs.[61]

CFSAN collects reports of AEs involving food, cosmetics, and dietary supplements in the CFSAN Adverse Event Reporting System (CAERS). A search of CAERS was conducted for AEs associated with Ta1 on April 22, 2024; the search yielded zero cases.

We did not identify any relevant case reports in the medical literature.

c. Clinical studies assessing safety

According to a book chapter from King and Tuthill (2016), over "4400 subjects have been enrolled in clinical trials conducted in US, Europe and China investigating the use of Ta1, including primary treatment for subjects with acute infections, such as seen in severe sepsis, and for chronic infections including chronic hepatitis B (CHB), chronic hepatitis C (CHC), and HIV; as an adjunct treatment for cancers, including melanoma, HCC, and NSCLC; and as an enhancement to both hepatitis B and influenza vaccines in immune-depressed individuals."[62] Over 17 million doses of Zadaxin (estimated as >350,000 individuals exposed) have been administered post market. Authors state that Zadaxin is generally well tolerated and over the "past 20 years, adverse experiences have been infrequent and mild."

[59] The FAERS search did not differentiate between Ta1 (free base) and Ta1 acetate.
[60] It is important to note that FAERS data have limitations. First, there is no certainty that the reported AE was due to the suspect product. FDA does not require that a causal relationship between a product and event be proven, and the report may not always contain enough detail to properly evaluate an event. Further, FDA does not receive all AE reports that may potentially occur with a product, especially for compounded products. Considering these limitations, FDA cannot make definitive conclusions regarding the safety of Ta1-related BDSs based on FAERS data alone.
[61] See label for peginterferon alfa-2a (Pegasys), BLA 103964/S-5276. Drugs@FDA, accessed 7/9/2024, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=103964.
[62] According to the acknowledgements, Robert King is an employee and Cynthia Tuthill is a consultant, for SciClone Pharmaceuticals (the manufacturer of Zadaxin).

A more recent article by Dinetz and Lee (2024) summarized Ta1 safety findings from several clinical studies in subjects with various infectious and oncologic diseases. Authors concluded that Ta1 has a "flawless safety record."

As noted in the nonclinical section (section II.C.1.a), due to a lack of well-defined dose-response relationships, it is difficult to determine the minimum Ta1 dose required to induce a pharmacological response. In an early phase 1 dose finding study, Ta1 (Hoffman-LaRoche; 2 mg/mL when reconstituted) was well tolerated after a single intramuscular (IM) dose of 0.6, 1.2, 2.4, 4.8, and 9.6 mg/m^2 in 14 subjects with advanced cancer.[63] One subject developed fever at 2.4 mg/m^2 and two subjects had mild nausea after 4.8 and 9.6 mg/m^2 doses. Per authors, despite failure to achieve a dose-limiting toxicity, escalation of Ta1 was stopped at the 9.6 mg/m^2 level since preliminary data suggested that immune responses were occurring in subjects treated with lower doses, no dose-immune response correlation was evident, and it was anticipated that further dose escalation would have encountered considerable practical difficulties related to diluent volume and number of injection sites (Dillman et al. 1982).

In clinical trials, Ta1 has been administered in daily doses ranging from 0.6 to 9.6 mg/m^2 (~1 to 16 mg assuming a mean BSA of 1.7 m^2), usually via SC administration on a biweekly schedule, for treatment periods ranging from 1 day to 12 months. The most common dose in clinical studies was 1.6 mg via SC administration. Ta1 has been used alone or in combination with antiviral and anticancer drugs. The most common AEs include local irritation, redness, and injection site discomfort (Dominari et al. 2020; Tao et al. 2023). In many studies, no AEs attributable to Ta1 use were reported.

There are potential safety concerns with administering Ta1 in patients who are undergoing deliberate immunosuppression. For example, in patients undergoing HSCT, which is one of the proposed uses, Ta1 could 1) develop or worsen acute graft-vs-host disease (GVHD) or chronic GVHD and 2) lead to engraftment failure (see Section II.D.10. for additional information on GVHD and engraftment failure). The AEs reported by Perruccio et al. (2010) are discussed below.

In the clinical trials that were considered in this evaluation of Ta1 as a vaccine adjuvant, although the authors concluded that Ta1 was well tolerated and no safety concerns were observed, there was limited description of the types of AEs, including serious AEs (SAEs). Some studies mentioned only pyrexia as the most common AE. The absence of descriptions of types of SAEs, time of occurrence of AEs with Ta1 use in relation to vaccination (for vaccines licensed in the United States), whether there was a dose-dependent effect, or information about resolution of AEs preclude FDA from drawing any conclusions that can contribute meaningfully regarding the safety of Ta1 when used with vaccines licensed for use in the United States. Adding an immunomodulatory product such as Ta1 to any vaccine could pose additional, significant safety concerns that warrant further evaluation in an adequate and well controlled clinical study. Further, lack of effectiveness of Ta1 when administered in conjunction with a vaccine licensed to prevent infectious disease (influenza) is viewed as a safety issue.

[63] For an average adult, doses of 0.6, 1.2, 2.4, 4.8, and 9.6 mg/m^2 translates to approximately 1, 2, 4, 8, and 16 mg assuming a mean BSA of 1.7 m^2.

Below we note a few other potential AEs as identified from the studies evaluated in Section II.D:

- Alanine aminotransferase (ALT) flares: In a study comparing Ta1 0.8 mg versus 1.6 mg twice weekly as monotherapy for 24 weeks in 316 subjects with CHB, there were 22 cases with transient exacerbation of liver function (11 cases in each dose group), which the authors referred to as ALT flares (Iino et al. 2005). Therapy was interrupted in 16 subjects. All subjects who experienced ALT flares recovered uneventfully and there were no cases of death due to liver failure. Per authors, a temporary elevation of ALT may occur when using a drug with a mechanism of intensifying the immune system and accelerating natural remission. The authors also noted that transient exacerbations of liver function may be seen in the natural progression of CHB.
- Thyroid stimulating hormone (TSH) abnormalities: In a study comparing treatment with a combination of Ta1 and interferon alpha-2b (IFN-alpha) versus IFN-alpha alone versus placebo in subjects with CHC, two subjects in the Ta1 and IFN-alpha group developed transient TSH depression followed by TSH elevation (Sherman et al. 1998). The authors note that this has been observed with IFN-alpha alone in other studies, but it is possible that the risk may be increased when Ta1 is combined with IFN-alpha.
- Nipple pain: In a study comparing treatment with transarterial chemoembolization (TACE) plus Ta1 or TACE alone in subjects with advanced HCC, only one AE (nipple pain) was identified as possibly or probably related to Ta1; nipple pain occurred in over 10% of Ta1 treated subjects (Gish et al. 2009).
- Fatal immune hemolytic anemia[64] after receiving Ta1 and donor lymphocyte infusion (DLI) to improve graft function and engraftment failure: Perruccio et al. (2010) reported that 1/6 (17%) of haplo-HSCT recipients, developed an immune hemolytic anemia after receiving DLI and Ta1 to improve the graft function. The subject subsequently died. This AE raises two concerns: (1) DLI is used in clinical practice to induce a graft versus leukemia effect and to improve engraftment. However, immune hemolytic anemia after HSCT occurs in less than 6% of HSCT recipients (Ahmed et al. 2015). It is unclear if Ta1 contributed to the severe and fatal immune reaction. This is especially concerning since there are immunogenicity concerns with Ta1 (see Section II.A. and Section II.C.2.d.). (2) Engraftment failure is a known AE after HSCT with a reported incidence of less than 4% (Mata et al. 2024). Although the authors did not clearly indicate whether the patient who received DLI developed graft failure, it appears that there was concern for poor graft function. The occurrence of graft failure in 1/6 patients (17%) appears excessive, and it raises concerns whether it is potentially related to Ta1 administration. However, those data are difficult to interpret due to insufficient sample size and lack of details.

d. Other safety information (e.g., relevant safety information from other regulatory Agencies as appropriate)

We searched for products containing Ta1 as an active ingredient licensed and marketed outside the United States with publicly available labels. The information below was abstracted from the websites for these products.

[64] Immune-mediated hemolytic anemia is a post-HSCT complication due to increased destruction of red blood cells.

Italy

Ta1 (Zadaxin) is authorized[65] in Italy as a 1.6 mg powder (1.6 mg/mL when reconstituted) for injection for SC or IM injection as an adjuvant to influenza vaccination in immunocompromised individuals.[66] Dosing is as follows: inject one vial, IM or SC, twice weekly for a period of four weeks, starting at time 0 (first vaccination). Repeat the treatment starting from the eighth week (second vaccination) up to the twelfth week. The label makes the following statements:

- Zadaxin should not be used in children.
- The product is also contraindicated during pregnancy and lactation.
- In subjects who are atopic[67] or have previously experienced allergic reactions, Zadaxin should be used with caution. In the case of subjects suffering from autoimmune diseases, the administration of Zadaxin must be evaluated on a case-by-case basis.
- Drug interactions: Thymosin alfa 1 acts on lymphocyte function. Caution should be exercised when Zadaxin is administered in combination with other immunomodulatory medicinal products.
- The administration of Zadaxin has not led to the appearance of clinically appreciable side effects, except for the occasional possibility of a modest and transient pain at the injection site.

Indonesia

Ta1 (Zadaxin) is registered[68] in Indonesia as a 1.6 mg powder for injection (1.6 mg/mL when reconstituted) for SC injection for the treatment of CHB in patients 18 years of age or older with compensated liver disease and hepatitis B virus replication (serum HBV DNA positive).[69] Dosing is as follows: 1.6 mg SC twice weekly with doses separated by 3 or 4 days. Therapy should be continued for six months (52 doses) without interruption. The label makes the following statements:

[65] To be marketed in Italy, a medicinal product must be granted a Marketing Authorisation (MA) by the Italian Medicines Agency or the European Commission. See https://www.aifa.gov.it/en/autorizzazione-dei-farmaci. Accessed June 25, 2024.
[66] See https://medicinali.aifa.gov.it/en/#/en/dettaglio/0000022315. Accessed June 25, 2024.
[67] Atopy refers to the genetic tendency to develop allergic diseases such as allergic rhinitis, asthma, and atopic dermatitis (eczema). Atopy is typically associated with heightened immune responses to common allergens, especially inhaled allergens and food allergens. See https://www.aaaai.org/tools-for-the-public/allergy,-asthma-immunology-glossary/atopy-defined. Accessed June 25, 2024.
[68] To be marketed in Indonesia, the Badan Pengawas Obat dan Makanan (BPOM) requires that all products be registered prior to their distribution. See https://ilaglobalconsulting.com/product-registration-indonesia/#:~:text=BPOM%20plays%20a%20crucial%20role,overseen%20by%20BPOM%20is%20thorough.
[69] See https://registrasiobat.pom.go.id/daftar-produk/assesment-report/33230. Accessed July 2, 2024.

- A transient increase in ALT to more than twice baseline value (flare) can occur during Zadaxin therapy. When ALT flare occurs, Zadaxin should generally be continued unless signs and symptoms of liver failure are observed.

- Because Zadaxin therapy appears to work by enhancing the immune system, it should be considered contraindicated in patients who are being deliberately immunosuppressed, for instance organ transplant patients, unless the potential benefits of the therapy clearly outweigh the potential risks.

- Zadaxin is well tolerated. During clinical experience involving over 2000 individuals with various diseases distributed over all age groups, no clinically significant adverse reactions attributable to Ta1 were reported (< 1% drug related adverse events). Adverse experiences have been infrequent and mild, consisting primarily of local discomfort at the injection site, and rare instances of erythema, transient muscle atrophy, polyarthralgia combined with hand edema, and rash.

Immunogenicity and Aggregation Concerns

FDA has issued a guidance regarding immunogenicity assessment for therapeutic protein products.[70] The guidance describes immunogenicity as the propensity of a therapeutic protein product to generate immune responses to itself and to related proteins including endogenous proteins or peptides, or to induce immunologically related adverse clinical events. Although the guidance addresses therapeutic protein products, concerns about immunogenicity are also relevant to peptides (such as Ta1 (free base) and Ta1 acetate), which can similarly elicit an immunogenic response; this immunogenic response may be enhanced when peptides are given via SC ROA. In general, the SC ROA is associated with increased immunogenicity compared to the IV ROA.

The consequences of triggering an immune response may range from antibody responses with no apparent clinical manifestations to life-threatening and catastrophic reactions. Such outcomes are often unpredictable in patients administered therapeutic protein or peptide products. One possible consequence of the development of an immune response is the development of neutralizing antibodies, which may lead to loss of efficacy or neutralization of the activity of the endogenous peptide counterpart.

Unlike small molecule APIs, peptides are distinct because they may have an inherent tendency to aggregate. Aggregation refers to the processes by which peptides associate into larger species consisting of multiple peptide chains. Aggregates can be highly ordered or amorphous and the formation can be reversible or irreversible (Zapadka et al. 2017). Peptides with as few as two amino acids have been shown to aggregate (Frederix et al. 2011). Aggregates can impact the pharmacology of the peptide. In addition, aggregation is a risk factor for immunogenicity and a decreased pharmacotherapeutic effect of the drug product due to effects on bioavailability, formation of precipitates, or anti-drug antibody production (Ratanji et al. 2014).

[70] See FDA's guidance for industry. *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014) available at https://www.fda.gov/media/85017/download.

As a peptide with 28 amino acids that is administered through the SC route of administration, Ta1 may pose a significant risk for immunogenicity, potentially amplified by aggregation as well as potential peptide-related impurities, as discussed above. The nomination did not include, and FDA is not aware of, information about Ta1 (free base) or Ta1 acetate to suggest that these substances do not present these risks.

The compounded drug product proposed in the nomination is a 3 mg/mL Ta1 solution for injection. We are unaware of data to support the compounding of the proposed 3 mg/mL strength product in humans. In our search of the literature, the highest strength of Ta1 identified to date in clinical studies was 2 mg/mL. One of the most important factors influencing the physical stability of peptides is peptide concentration (Zapadka et al. 2017). It is possible that a more concentrated solution of Ta1 could lead to aggregation, and therefore, increased immunogenicity potential.

e. Therapies that have been used for the condition(s) under consideration

There are FDA-approved drug products that treat many of the same medical conditions as those evaluated for the Ta1 compounded drug product.[71] See subsection c. in Sections II.D.1-12 for information on currently available FDA-approved drug products indicated for the medical conditions considered in this evaluation.

Conclusions:

Based on the available information for Ta1 (free base) and Ta1 acetate, we conclude that the use of Ta1-related BDSs in compounding may raise safety concerns.

In most clinical studies, Ta1 has been found to be well-tolerated and not associated with significant AEs attributable to Ta1 when administered in doses in the range of 1-16 mg via the SC ROA for up to 12 months. The most common dose in clinical studies was 1.6 mg via SC administration. The most common adverse reactions reported are local irritation, redness, or discomfort at the injection site. Information in the labels of Ta1 products marketed outside the United States includes warnings and contraindications when used in children, pregnant and lactating women, subjects with autoimmune diseases, and immunosuppressed populations. The Ta1 product label for Zadaxin in Indonesia includes information on transient increases in liver enzymes (characterized as flares) and recommendations about continuing Ta1 administration.

Although Ta1 has been found to be well-tolerated and not associated with significant AEs attributable to Ta1 in the literature, there may be concerns about its clinical use in compounding. For example, it is not clear whether the administration of Ta1 in patients undergoing HSCT could lead to the development or worsen acute GVHD or chronic GVHD and/or lead to engraftment failure. In addition, based on the data considered, safety data are insufficient to evaluate the risks associated with the use of Ta1 as a vaccine adjuvant with influenza vaccines licensed for use in the United States without an adequate assessment of risks, considering that the

[71] FDA considers the existence of FDA-approved or OTC monograph drug products to treat the same condition as that proposed for the nomination relevant to FDA's consideration of the safety criterion, to the extent there may be therapies that have been demonstrated to be safe under the conditions of use set forth in the approved labeling. See 84 FR 4696.

nominator of Ta1 is proposing for use in individuals with a depressed response, such as in the elderly, and as well as the lack of assessment of the optimal Ta1 dose and regimen.

The safety profile of compounded drug products containing Ta1 can be negatively impacted by various factors, including but are not limited to, the product formulation, peptide concentration, and storage conditions favoring the generation of product-related impurities and/or peptide aggregates capable of inducing untoward immunogenic responses. 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 and 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.

In addition, we are unaware of data to support the proposed 3 mg/mL strength Ta1 drug product. The highest strength of Ta1 administered in clinical trials to date is 2 mg/mL, and it is possible that a more concentrated solution could lead to aggregation and therefore increased immunogenicity potential.

At the time of this evaluation, there are several currently available FDA-approved drug products indicated to treat many of the medical conditions reviewed in this evaluation.

D. Are there concerns about whether a substance is effective for a particular use?

The following databases were consulted in the preparation of this section: PubMed, EMBASE, Cochrane Database of Systematic Reviews, ClinicalTrials.gov, the websites of professional healthcare organizations, and various online clinical references and websites. All publicly available English full text articles were considered. We do not consider articles with English abstracts with the full text in a foreign language. Of note, the nomination did not include any articles with a verified English translation.[72] The clinical articles included in the nomination and those identified by FDA do not always clearly identify Ta1 as a free base or salt. Therefore, in this section, the substance will be generally referred to as Ta1, unless the article under discussion clearly specifies the use of the free base or the acetate salt in a study. In addition to a review of pertinent information from these databases, this section provides a brief overview of the uses of Ta1 evaluated.

We evaluated Ta1 (free base) and Ta1 acetate for hepatitis B, hepatitis C, HIV, COVID-19, depressed response to vaccinations; adjuvant to flu vaccines, malignant melanoma, HCC,

[72] See 21 CFR 10.20(c)(2) ("If a part of the material submitted is in a foreign language, it must be accompanied by an English translation verified to be complete and accurate, together with the name, address, and a brief statement of the qualifications of the person making the translation. A translation of literature or other material in a foreign language is to be accompanied by copies of the original publication.")

NSCLC, sepsis, infections after HSCT, COPD, and ME/CFS and considered available data to support effectiveness.

1. *Hepatitis B*

HBV infection is a vaccine-preventable liver infection. Acute HBV is a short-term illness that occurs within the first 6 months after exposure to HBV and may lead to chronic HBV infection (CHB). CHB is a lifelong infection which can cause liver damage, cirrhosis, liver cancer (HCC), and death. HBV infection may be asymptomatic and may progress to symptomatic infection with abdominal pain, jaundice, or with other manifestations secondary to advanced liver disease and HCC.[73]

Serologic markers are used to diagnose and distinguish between acute and chronic infections (Tang et al. 2018). HBV laboratory tests include the following:[74]

- HBV DNA—indicates active infection (acute or chronic)
- HBV surface antigen (HBsAg)—indicates infection (either acute or chronic)
- HBV surface antibody (HBsAb)—indicates immunity to HBV
- HBV e antigen (HBeAg)—associated with high infectivity, variably present
- HBV e antibody (anti-HBe)—associated with declining HBeAg titers, indicating a favorable immune response to HBV infection
- HBV core antibody (anti-HBc)—indicates past or current HBV infection

There are no FDA-approved drug products for acute HBV infection.[75,76] There are several FDA-approved therapies for the treatment of CHB. As CHB may cause cirrhosis, HCC, and death, the goals of treatment are to reduce the risk of progression to cirrhosis and liver-related complications, including HCC. In clinical practice, sustained HBV DNA suppression and clearance of HBsAg are often used to assess therapeutic effect (Terrault et al. 2018).

For CHB, the FDA-approved treatment options are broadly classified as either immunomodulatory agents (i.e., recombinant human alpha interferons (IFNs)) or antiviral agents (nucleoside/nucleotide analogue reverse transcriptase inhibitors (NrtIs)).[77] Currently available therapies achieve sustained suppression of HBV DNA while on treatment, but rates of HBsAg loss with or without seroconversion to HBsAb remain low.[78] The 2018 clinical guidance of the

[73] Hepatitis B Basics, Centers for Disease Control and Prevention (CDC) website, accessed 5/30/2024, https://www.cdc.gov/hepatitis-b/about/index.html.
[74] Hepatitis B Online is a free educational website from the University of Washington Infectious Diseases Education & Assessment program, funded by CDC. See: HBV Screening, Testing, and Diagnosis, Hepatitis B Online website, accessed 6/12/2024, https://www.hepatitisb.uw.edu/go/screening-diagnosis/diagnosis-hbv/core-concept/all.
[75] Treatment of Hepatitis B, CDC website, accessed 5/30/2024, https://www.cdc.gov/hepatitis-b/treatment/index.html.
[76] Antiviral therapy is generally not necessary in symptomatic acute HBV infection because >95% of immunocompetent adults recover spontaneously. However, antiviral therapy is recommended by professional clinical organizations in certain settings, such as acute liver failure (Terrault et al. 2018).
[77] Choosing an Initial HBV Treatment Regimen, Hepatitis B Online website, accessed 6/3/2024, https://www.hepatitisb.uw.edu/go/hbv/medications-used-to-treat-hbv/core-concept/all.
[78] See final guidance for industry entitled, Chronic Hepatitis B Virus Infection: Developing Drugs for Treatment at https://www.fda.gov/media/117977/download.

American Association for the Study of Liver Diseases (AASLD)[79] lists the following preferred therapies for CHB in adults:

- Antiviral agents, NrtIs entecavir (ETV), tenofovir alafenamide (TAF), and tenofovir disoproxil fumarate (TDF)

  NrtIs are typically administered long-term or lifelong. Clinical studies have shown that 68-90% of persons with CHB who are treated with oral ETV, TAF, or TDF will achieve undetectable HBV DNA levels after 48 weeks of therapy;[80] cut-offs to define HBV DNA suppression have ranged <29-60 IU/mL (Terrault et al. 2018). Overall, oral antivirals have been shown to reduce the risk of cirrhosis, decompensated liver disease, and HCC; however, these agents are limited in their ability to clear the virus.[81,82] A major concern with long-term NrtI treatment is the development of antiviral resistance. Among the NrtI therapies, ETV, TAF, and TDF have very low rates of drug resistance in NrtI-naïve persons with CHB, and TAF and TDF have low rates of drug resistance in NrtI-experienced persons with CHB. In contrast, the NrtIs adefovir, lamivudine, and telbivudine[83] are associated with a low barrier to HBV resistance[84] and are categorized as non-preferred options (European Association for the Study of the Liver (EASL) 2017; Terrault et al. 2018).

- Pegylated interferon alpha-2a (PEG-IFN)[85]

  Rates of HBV DNA suppression have ranged from 8-43% with PEG-IFN depending on HBeAg status and the cutoff to define HBV DNA suppression (Terrault et al. 2018). PEG-IFN is typically administered for a finite duration (typically 48 weeks) as a SC

[79] AASLD develops evidence-based practice guidelines which are updated regularly. The 2018 guidance was developed by consensus of an expert panel and was intended to complement the 2016 AASLD guidelines for the treatment of CHB, which conducted systematic reviews and used a multidisciplinary panel of experts to rate the quality of the evidence and the strength of each recommendation. See: Practice Guidelines, AASLD website, accessed 5/30/2024, https://www.aasld.org/practice-guidelines.
[80] Choosing an Initial HBV Treatment Regimen, Hepatitis B Online website, accessed 6/9/2024, https://www.hepatitisb.uw.edu/go/hbv/medications-used-to-treat-hbv/core-concept/all.
[81] Choosing an Initial HBV Treatment Regimen, Hepatitis B Online website, accessed 6/9/2024, https://www.hepatitisb.uw.edu/go/hbv/medications-used-to-treat-hbv/core-concept/all.
[82] Complete HBV eradication or virological cure is limited by integration of HBV DNA into the host genome and a reservoir of covalently closed circular DNA (cccDNA) established in hepatocytes infected with HBV (Lok et al. 2017; Tang et al. 2018).
[83] Telbivudine drug products have been discontinued (See: FDA Orange Book, accessed 6/9/2024, https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm).
[84] The genetic barrier to resistance refers to the number of mutations that the virus must accumulate in order to replicate efficiently in the presence of the antiviral agent. An agent with a high barrier will have a lower likelihood of developing resistance (Ghany and Doo 2009).
[85] Pegylated interferon has replaced standard IFN, as pegylation reduces the rate of absorption following subcutaneous injection, as well as renal and cellular clearance and immunogenicity. These effects enhance the half-life of PEG-IFN, allowing it to be dosed less frequently. In addition, some studies have shown higher rates of response with PEG-IFN as compared to standard IFN. See: Pegylated interferon for treatment of chronic hepatitis B virus infection, UptoDate website, accessed 6/17/2024, https://www.uptodate.com/contents/pegylated-interferon-for-treatment-of-chronic-hepatitis-b-virus-infection.

injection.[86] PEG-IFN is preferred over nonpegylated forms for simplicity (Terrault et al. 2018).[87]

When initiating treatment for CHB, the recommended approach in most circumstances is to use a potent NrtI that has a high barrier to resistance, typically with long-term administration of the medication. Combination therapy, including use of two oral NrtIs or one NrtI plus PEG-IFN, is not recommended for initial treatment except in certain circumstances.[88]

Sustained HBV DNA suppression is associated with serum ALT normalization and improvement in liver histology, including regression of hepatic fibrosis and cirrhosis. Hence, sustained HBV DNA suppression off-treatment is considered an appropriate efficacy endpoint in clinical trials evaluating finite-duration therapies.[89] In addition, clearance of HBsAg is associated with reduced risk of hepatic decompensation and improved survival; therefore, sustained suppression of HBV DNA off treatment with HBsAg loss is also an appropriate primary efficacy endpoint to evaluate finite duration therapies. Currently available therapies achieve sustained suppression of HBV DNA while on treatment, but rates of HBsAg loss with or without seroconversion to HBsAb remain low. Secondary efficacy endpoints such as HBeAg loss, anti-HBe seroconversion in HBeAg-positive patients, and ALT normalization are also of interest.[90]

Ta1 is not mentioned for the treatment of CHB in 2016 AASLD guidelines (Terrault et al. 2016), 2017 EASL guidelines (EASL 2017), 2018 AASLD guidance (Terrault et al. 2018), or 2024 World Health Organization (WHO) guidelines for CHB (WHO 2024). While the 2012 version of the clinical guidelines published by the Asian Pacific Association for the Study of the Liver (APASL) recommended the use of Ta1 as an alternative to IFN or PEG-IFN, the 2016 (most recent) APASL guidelines only acknowledge that Ta1 as an immunomodulatory agent that has been licensed in some Asian countries, and Ta1 is not listed under recommended treatment (Liaw et al. 2012; Sarin et al. 2016).

a. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

The nomination cited references that discussed Ta1 for the treatment of HBV infection, including three clinical trials (Chien et al. 1998; You et al. 2001;[91] You et al. 2006), two literature reviews

[86] Choosing an Initial HBV Treatment Regimen, Hepatitis B Online website, accessed 6/11/2024, https://www.hepatitisb.uw.edu/go/hbv/medications-used-to-treat-hbv/core-concept/all.
[87] The 2018 AASLD clinical guidance document lists IFN-alpha-2b as a preferred drug for children, while noting that PEG-IFN-alpha2a is not approved for children with CHB but is approved for treatment of chronic hepatitis C. However, indications for PEG-IFN-alpha2a now include pediatric patients with CHB (See: See label for peginterferon alfa-2a (Pegasys), BLA 103964/S-5276. Drugs@FDA, accessed 5/20/2024, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=103964.)
[88] Choosing an Initial HBV Treatment Regimen, Hepatitis B Online website, accessed 6/25/2024, https://www.hepatitisb.uw.edu/go/hbv/medications-used-to-treat-hbv/core-concept/all.
[89] See final guidance for industry entitled, Chronic Hepatitis B Virus Infection: Developing Drugs for Treatment at https://www.fda.gov/media/117977/download.
[90] See final guidance for industry entitled, Chronic Hepatitis B Virus Infection: Developing Drugs for Treatment at https://www.fda.gov/media/117977/download.
[91] You et al. 2001 was considered to be a duplicate publication of You et al. 2006 in a meta-analysis by Yang et al. 2008.

(Chien and Liaw 2004; Tuthill and King 2013), and information from the International Peptide Society (IPS) on the use of Zadaxin. The nomination did not specify whether the proposed Ta1 drug products are intended to treat acute or chronic HBV infection; however, it included references focused on CHB. We also searched the medical literature on the use of Ta1 for the treatment of HBV infection/CHB and retrieved additional publications. The key findings of selected publications identified in the FDA search and those included in the nomination are summarized below. To evaluate Ta1 for CHB, discussions were grouped together as follows: studies of Ta1 monotherapy, studies of Ta1 monotherapy versus IFN-alpha, studies of Ta1 in combination with PEG-IFN, and studies of Ta1 in combination with NrtIs. The Ta1 dosing regimen was 1.6 mg administered via SC injection twice weekly unless otherwise noted.

Studies which evaluated Ta1 monotherapy

Chan et al. (2001) conducted a meta-analysis of five randomized controlled trials (RCTs) comparing thymosin[92] to placebo or "usual care" for subjects with CHB (HBeAg positive and negative) (Mutchnick et al. 1992 (abstract); Chien et al. 1998; Chow et al. 1998 (abstract); Mutchnick et al. 1999; Zavaglia et al. 2000). The meta-analysis is limited by heterogeneity across the clinical studies that were analyzed; differences included: one study did not evaluate Ta1 monotherapy, a lack of uniformity of the HBV DNA assays used across studies, and differences in inclusion criteria (including HBeAg status) and virological response endpoints. The key findings reported from the meta-analysis were that the odds ratio (95% confidence interval (CI)) of the virological response (defined as the reduction of HBV DNA to undetectable levels plus the loss of HBeAg if a patient was HBeAg-positive before treatment) of thymosin over placebo at the end of treatment, 6 months post-treatment, and 12 months post-treatment were 0.56 (0.2-1.52), 1.67 (0.83-3.37) and 2.67 (1.25-5.68), respectively. Per authors, "[t]hese results suggest that there is a lack of sufficient evidence to indicate that thymosin may affect the clearance of HBV replication markers at the end of treatment and 6 months post-treatment"; however, the authors concluded that thymosin is effective in suppressing viral replication in CHB 12 months after treatment cessation. Given the limitations stated above, FDA evaluated the individual studies which were included in the Chan et al. 2001 meta-analysis of Ta1 monotherapy. Additional details about the individual trials are discussed below. We do not discuss Mutchnick et al. 1992 or Chow et al. 1998 in further detail because only abstracts could be located. In addition, Mutchnick et al. 1992 evaluated both Ta1 and thymosin fraction 5 (TF5)[93] in a combined "thymosin" group.

Chien et al. (1998) evaluated subjects with CHB (HBeAg positive) who received Ta1 for 26 weeks (group A, n=32) or 52 weeks (group B, n=34), or no treatment (group C, n=32) for 18 months in a RCT. The proportion of subjects with HBV DNA and HBeAg levels reduced to below the level of detection was higher in group A (40.6%) and group B (26.5%) than group C (9.4%) at 18 months (group A versus C, p =0.004), although rates between the three groups were similar at the end of therapy. The authors noted that there was a trend for the virological response

[92] Four trials used Ta1 (900 μg/m^2 BSA or 1.6 mg SC twice weekly), and the remaining trial used both Ta1 and thymosin fraction 5 (TF5) (90 μg/m^2 SC twice weekly). TF5 is a partially purified extract of bovine thymus containing at least 40 peptide components. According to authors, the known biological effects of TF5 and Ta1 are similar (Mutchnick et al. 1991).
[93] Ibid.

to increase after the end of Ta1 therapy and that none of the responders achieved HBsAg loss. All biopsy specimens from the 55 subjects who consented to undergo biopsy (group A n=22, group B n=17, group C n=16) were positive for HBsAg pre- and post-treatment. Histological assessment performed by a pathologist blinded to treatment groups showed a significant improvement in Ta1-treated subjects, particularly in lobular necroinflammation and scores excluding fibrosis. The authors concluded that the results suggested that a 26-week course of Ta1 therapy was effective in patients with CHB; however, we note that the study limitations included small study size, lack of blinding except for the histology assessment, and a DNA quantification assay with a limit of detection (1.5 pg/mL or approximately 400,000 copies/mL (Kuhns et al. 1989)) several logs higher than current standards used for currently approved drugs, i.e., the assays used for quantification of HBV DNA were much less sensitive than current assays used, and it is unclear whether similar results would be obtained with current, more sensitive assays.[94] We also note that our interpretation of many older studies, such as Chien et al. 1998, is complicated by use of a composite endpoint such as undetected HBV DNA and HBeAg, or undetected HBV DNA and ALT normalization.

Mutchnick et al. (1999) evaluated subjects with CHB (HBeAg positive) in a R, DB, placebo-controlled (PC) trial. Subjects received Ta1 (n=49) or placebo (n=48) for 6 months, with 6-month follow-up. A complete response to treatment was defined as HBV DNA reduced to below the limit of detection during the 12-month study, with undetected HBV DNA and negative HBeAg serology at 12 months; the primary endpoint (complete response composite endpoint at 6 months post-treatment) did not meet statistical significance. A complete response was observed in 7/49 (14%) subjects in the Ta1 group and 2/48 (4%) in the placebo group (p=0.084). Reactivation of disease, as defined by reappearance of serum HBV DNA, occurred in 2/7 subjects with complete response to Ta1 and 0/2 of the placebo group. Five (10%) subjects in the Ta1 group and four (8%) in the placebo group exhibited a delayed response (undetected HBV DNA levels achieved after the 12-month study period, during long-term follow-up (15-44 months), with undetected HBV DNA and negative HBeAg serology values at the last assessment). Rates of undetected HBV DNA at 12 months were 20% (Ta1 group) and 21% (placebo group), and rates of undetected HBeAg were 23% (Ta1) and 15% (placebo). A total of 12 (25%) subjects in Ta1 group and six (13%) in the placebo group showed undetected HBV DNA with negative HBeAg serology during or following the 12-month study period (p<0.11). None of the subjects in either treatment group became HBsAg negative during the initial study period. One subject who received Ta1 and had a complete response to treatment, and one subject who received placebo and exhibited a delayed response, became HBsAg negative during long-term follow-up (at months 37 and 30, respectively). The authors stated that, although there was a trend towards efficacy, "these results do not confirm observations of treatment efficacy reported in other clinical studies." Of note, the assay used to define undetected HBV DNA had a limit of detection (1.5 pg/mL or approximately 400,000 copies/mL (Kuhns et al. 1989)) several logs higher than the current standards used for approved drugs.

Zavaglia et al. (2000) evaluated subjects with CHB (anti-HBe positive) who received either Ta1 (900 µg/m^2 BSA SC twice weekly, n=22) or no treatment (control group, n=22) for 6 months,

[94] In contrast to the assays used in the referenced studies, most HBV DNA assays used for approvals and now currently used in clinical practice utilize reverse-transcriptase polymerase chain reaction technology with a sensitivity of 5-80 IU/mL (25-400 copies/mL) and a dynamic range up to 7 $\log_{10}$ IU/mL (Terrault et al. 2018).

with follow-up ranging from 12-32 months, in a RCT. Six months after completion of therapy, undetected HBV DNA and ALT normalization were observed in 14% of the Ta1 group and 4.5% of the control group. The rate of undetected HBV DNA at six months after therapy completion was 18% in both groups, and at the end of follow-up (median follow-up 20 months after treatment ended) was 23% in the Ta1 group and 14% in the control group. No subject became HBsAg negative. The authors concluded that in patients with anti-HBe CHB, Ta1 therapy alone does not increase the response rate, but may contribute to reduced immune-mediated liver cell necrosis. The limitations of this study include its small size, lack of blinding, and use of an HBV quantification assay with a limit of detection (1.5 pg/mL or approximately 400,000 copies/mL (Kuhns et al. 1989)) several logs higher than the current standards used for approved drugs.

Arase et al. (2003) evaluated Japanese subjects with CHB (N=16) who received Ta1 (0.8 mg, n=8) or Ta1 (1.6 mg, n=8) administered SC six times weekly for 2 weeks, followed by twice weekly for 22 weeks, in a R trial. Response was defined as HBeAg and HBV DNA reduced to undetected levels and ALT normalization 24 months after initiation of Ta1 therapy. The response rate was 37.5% (6/16 subjects); the difference between low- and high-dose groups was not statistically significant (p=0.068). The authors observed that all subjects with a response after Ta1 therapy showed a slight or severe fluctuation pattern of serum ALT level. HBsAg data were not discussed in the publication. The authors concluded that a 24-week course of Ta1 could be a worthwhile strategy for patients with CHB with a serum HBV DNA of less than 100 milliequivalents/mL, and patients with transient acute exacerbation (ALT elevation) during Ta1 therapy often respond well. The study limitations included small size, lack of blinding, lack of control group, and use of an HBV quantification assay with a limit of detection (700,000 copies/mL) higher than current standards used for approved drugs. Data for HBV DNA suppression were not individually presented in the publication.

Iino et al. (2005) evaluated Japanese subjects with CHB (HBeAg positive) who received Ta1 (0.8 mg SC, n=139) or Ta1 (1.6 mg SC, n=144) for 24 weeks in a R trial.[95] Subjects received treatment six times per week for the first 2 weeks, then twice weekly for the next 22 weeks. Twelve months after cessation of therapy, 36.4% of the higher-dose group achieved normalization of ALT, 30% achieved reduction of HBV DNA to below the limit of detection by branched DNA assay (15% by transcription-mediated amplification[96]), and 22.8% achieved reduction of HBeAg to undetected levels. Subjects in the lower-dose group showed similar outcomes. HBsAg data were not discussed in the publication. The authors noted two cases of HCC, which per authors may have been facilitated by the high prevalence of subjects with advanced disease. ALT flares were seen in 22 patients and therapy with Ta1 was interrupted in 16, but all patients recovered or had their flares managed by hospitalization. The authors noted that transient exacerbations of liver function are commonly seen in the natural progression of CHB and that ALT flares are an essential component of natural remission. Although the authors concluded that, "Ta1 at doses of 0.8 and 1.6 mg exhibits long-term efficacy against hepatitis B with a good safety profile", we note that the study limitations included lack of blinding, lack of a control group, and use of HBV quantification assays with detection limits (700,000 copies/mL

[95] Due to a lack of stratification based on liver histology, the 1.6 mg-treatment group had a higher ratio of advanced fibrosis and inflammation.

[96] During the course of the study, the more sensitive transcription-mediated amplification (TMA) assay became available for the determination of HBV DNA level, so the authors provided HBV DNA levels from both assays.

for the branched DNA assay and ~5,000 copies/mL for the transcription-mediated amplification assay) higher than the current standards used for approved drugs.

Studies which evaluated Ta1 monotherapy versus IFN-alpha

It is important to note that PEG-IFN has replaced use of standard IFN. Several studies have shown that PEG-IFN is more effective than standard IFN with respect to serologic and virologic outcomes with treatment of HBV. In addition, PEG-IFN is better tolerated than standard IFN and requires less frequent dosing.[97] The marketing of standard IFN-alpha products has been discontinued in the United States; however, these studies still provide information about Ta1 as monotherapy, even if the comparator is no longer the standard treatment.[98]

Yang et al. (2008) conducted a meta-analysis of four trials (Andreone et al. 1996b; Zhuang et al. 2001; You et al. 2005; You et al. 2006) that compared the efficacy of Ta1 to IFN-alpha for the treatment of CHB. The meta-analysis is limited by comparison of Ta1 to IFN-alpha, which, as noted above, is an inappropriate control as it is no longer recommended/marketed in the United States. Additional limitations include that, it is unclear if the historical control was appropriately matched with participants in the investigational treatment arms, there was a lack of blinding, no trials described the method used to generate the allocation sequence, and different HBV DNA assays were used. The definitions used in this meta-analysis and the included studies were:

- Virological response - reduction of HBV DNA to undetected levels plus transition to negative HBeAg serology if subjects were HBeAg-positive before treatment
- Biochemical response - normalization of ALT levels
- Complete response - fulfilling both biochemical and virological responses

The key findings of the meta-analysis were that the ORs (95% CI) of the virological response, biochemical response, and complete response of Ta1 over IFN-alpha at the end of 6 months treatment were 0.62 (0.35-1.10), 0.60 (0.34-1.05) and 0.54 (0.30-0.97), respectively. The ORs (95% CI) of the virological response, biochemical response, and complete response of Ta1 over IFN-alpha at the end of follow-up (6 months post-treatment) were 3.71 (2.05-6.71), 3.12 (1.74-5.62) and 2.69 (1.47-4.91), respectively. Per authors, these data showed that compared with IFN-alpha, the benefit of Ta1 was not immediately significant at the end of therapy, but responses had a tendency to increase or accumulate gradually after therapy. The authors noted that the inter-trial heterogeneity was not statistically significant ($p>0.1$) and the effect remained significant when a random-effects model was used. HBsAg data were not discussed in this publication. Given the limitations stated above, FDA evaluated the studies included in the Yang et al. (2008) meta-analysis; these studies are discussed in further detail below.

Andreone et al. (1996b) evaluated subjects with CHB (anti-HBe positive) in a RCT. Subjects received Ta1 (900 µg/m^2 BSA SC twice weekly) (n=17) or IFN-alpha (5 million units (MU) SC three times weekly) (n=16) for 6 months, with 6-month follow-up. Fifteen subjects with similar virological and clinical characteristics who were followed up for at least 12 months were used as

[97] Choosing an Initial HBV Treatment Regimen, Hepatitis B Online website, accessed 6/21/2024, https://www.hepatitisb.uw.edu/go/hbv/medications-used-to-treat-hbv/core-concept/all.
[98] See: FDA Purple Book, accessed 6/18/2024, https://purplebooksearch.fda.gov/.

a historical control (HC) group. Complete response occurred in 5/17 (29.4%) subjects in the Ta1 group and 7/16 (43.8%) in the IFN group at the end of 6 months' treatment, and 7/17 (41.2%) in the Ta1 group and 4/16 (25%) in the IFN group after the 6-month follow-up (not statistically significant per authors). At the end of treatment, HBV DNA was undetected in 9/17 (52.9%) in the Ta1 group and 10/16 (62.5%) in the IFN group; at follow-up, 10/17 (58.8%) of the Ta1 group, 6/16 (37.5%) of the IFN group, and 1/16 (6.7%) of the HC group had undetected HBV DNA. Compared with the HC group, the authors stated that a higher rate of complete response occurred in the IFN group at the end of therapy, and in the Ta1 group at the end of follow-up. HBsAg data were not discussed in the publication. There were no statistically significant intragroup or intergroup differences in histology scores, as assessed by a pathologist blinded to the treatment allocation. The limitations of this study included its small size, lack of blinding except for the histology assessment, and use of an HBV assay with a limit of detection (1 pg/mL or approximately 300,000 copies/mL (Kuhns et al. 1989)) several logs higher than current standards used for approved drugs.

Zhuang et al. (2001) evaluated Chinese subjects with CHB (anti-HBe positive) who received Ta1 (n=18) or IFN-alpha (3-5 MU SC injection daily for 15 days, then three times weekly, n=30) for 6 months, with 6-month follow-up, in a R study. Thirty subjects with the same virological and clinical characteristics, never treated with IFN-alpha, comprised the HC group. At 6 months, nine (50%) subjects had undetected HBV DNA in the Ta1 group versus 18 (60%) in the IFN-alpha group; at 12 months, 12 (66.7%) of subjects had undetected HBV DNA in the Ta1 group versus nine (30%) in the IFN-alpha group. In the HC group, two (6.7%) subjects had undetected HBV DNA at 6 and 12 months. Complete response at 12 months was observed in 10/18 subjects (55.6%) in the Ta1 group, 7/30 (23.3%) in the IFN-alpha group, and 1/30 (3.3%) in the HC group (Ta1 versus IFN-alpha, $p<0.05$, Ta1 versus HC, $p<0.01$). HBsAg data were not discussed in the publication. The authors noted that the benefit of Ta1 was not immediately apparent at the end of therapy. The limitations of this study included its small size, lack of blinding, and an unidentified HBV DNA qualitative assay for which performance data were not reported.

You et al. (2005) evaluated subjects with CHB (anti-HBe positive) who received Ta1 (n=26) or IFN-alpha (5 MU SC daily for 15 days, then three times per week for 6 months, n=30) in a R trial. Thirty subjects followed for 12 months served as a retrospective HC group. At the end of treatment, complete response occurred in 8/26 (30.8%) subjects in the Ta1 group and 14/30 (46.7%) subjects in the IFN-alpha group. After 6 months of follow-up, 11/26 (42.3%) subjects in the Ta1 group and 7/30 (23.3%) subjects in the IFN-alpha group had complete response. The rates of HBV DNA reduced to undetected levels at 6 months were 46.2% (Ta1 group) and 60% (IFN-alpha group), and at the 6-month follow-up were 61.5% (Ta1) and 30% (IFN-alpha) ($p<0.05$ versus IFN-alpha). In the HC group, undetected HBV DNA (<500 copies/mL) was achieved by 6.7% of the subjects at the 6- and 12-month follow-ups. HBsAg data were not discussed in the publication. The authors concluded that the results suggested that a 6-month course of Ta1 therapy was effective in patients with anti-HBe-positive CHB, and as compared with IFN-alpha, seemed to induce a gradual and more sustained normalization of ALT and suppression of HBV DNA. The study limitations included its small size, lack of blinding,

comparison with an HC group, and use of an unidentified quantitative assay with no description of the methodology and limited performance characteristics.

You et al. (2006) evaluated Chinese subjects with CHB (HBeAg positive) who received Ta1 (n=29) or IFN-alpha (5 MU daily for 15 days, then three times weekly, n=33) for 6 months, with 6-month follow-up, in a R trial. Thirty subjects served as an HC group. At the end of therapy (6 months), 16/29 (55.2%) subjects in the Ta1 group, 22/33 (66.7%) in the IFN-alpha group, and 2/30 (6.7%) in the HC group had undetected HBV DNA; complete response occurred in nine (31%) subjects in the Ta1 group and 15 (45.5%) in the IFN-alpha group. At 12 months, 21/29 (72.4%) subjects in the Ta1 group, 13/33 (39.4%) in the IFN-alpha group, and 2/30 (6.7%) in the HC group had undetected HBV DNA ($p<0.01$ versus IFN-alpha, $p<0.001$ versus HC). Complete response was observed in 14 (48.3%) subjects in the Ta1 group and nine (27.3%) subjects in the IFN-alpha group ($p>0.05$). HBsAg data were not discussed in the publication. The authors noted that the benefit of Ta1 was not immediately significant at the end of therapy and complete virological response had a tendency to increase or accumulate gradually after therapy. The authors concluded that the results suggested that a 6-month course of Ta1 therapy is effective in patients with CHB. Limitations of this study included its use of an HC group, small size, lack of blinding, and an unidentified HBV DNA quantification assay with a stated limit of 1,000 copies/mL (performance data not provided).

Studies which evaluated Ta1 in combination with PEG-IFN

Ta1 has also been evaluated in combination with IFNs (e.g., lymphoblastoid IFN, IFN-alpha2b, PEG-IFN-alpha2a) for the treatment of CHB. We note again that PEG-IFN has replaced standard IFN; PEG-IFN is better tolerated, requires only weekly dosing, and several studies have shown that PEG-IFN is more effective than standard IFN with respect to serologic and virologic outcomes with treatment of HBV.[99] Standard IFN-alpha products have been discontinued.[100] Therefore, studies in which Ta1 was evaluated in combination with PEG-IFN are more relevant in light of current therapies.

Song et al. (2011) conducted a retrospective analysis of data obtained from subjects with CHB (HBeAg positive) who received PEG-IFN monotherapy (180 µg SC once per week, n=17) for 48 weeks, or PEG-IFN for 48 weeks in combination with Ta1 for the first 12 weeks (PEG/Ta1, n=20) in an RCT. The aim of this study was to investigate whether serum levels of HBsAg correlate with serum levels of HBV DNA and if they can predict the treatment response to PEG-IFN treatment with or without Ta1. Virologic response was defined as HBV DNA < 2000 IU/mL (approximately 12,000 copies/mL). Rates of virologic response at week 48 were 6/17 (35%) subjects in the monotherapy group and 8/20 (40%) subjects in the PEG/Ta1 group; at week 96, rates were 2/14 (14%) for monotherapy and 4/19 (21%) for PEG/Ta1. At week 48, rates of HBeAg seroconversion were 35% in the monotherapy group and 40% in the PEG/Ta1 group; at week 96, rates were 43% for monotherapy and 53% for PEG/Ta1. The response rate was not statistically different according to the two treatment arms. No subjects showed a loss of HBsAg or anti-HBs seroconversion. The authors observed that a decrease to <60% of baseline levels of

[99] Choosing an Initial HBV Treatment Regimen, Hepatitis B Online website, accessed 6/21/2024, https://www.hepatitisb.uw.edu/go/hbv/medications-used-to-treat-hbv/core-concept/all.
[100] See: FDA Purple Book, accessed 6/18/2024, https://purplebooksearch.fda.gov/.

HBsAg at week 12 was identified as an independent predictive factor for HBeAg seroconversion at week 96; however, the utility of reduction in HBsAg from baseline (without complete clearance) for assessing response to CHB therapies is unclear because of inconsistent correlations between quantitative HBsAg and clinical response.[101] The study limitations included retrospective analysis of data and an HBV DNA cut-off much higher than current standards used for currently approved drugs, i.e., the assays used for quantification of HBV DNA were much less sensitive than current assays used, and it is unclear whether similar results would be obtained with current, more sensitive assays.

Kim et al. (2012) evaluated subjects with CHB (HBeAg positive) who received PEG-IFN monotherapy (180 µg SC weekly for 48 weeks) (PEG group, n=25), or PEG-IFN for 48 weeks in combination with Ta1 (1.6 mg SC twice weekly for the first 12 weeks) (PEG/Ta1, n=26), with 48-week follow-up, in a R, open label (OL) study. At week 48, 11 subjects (42.3%) in the PEG/Ta1 group and 10 (40%) in the PEG group achieved serum HBV DNA <20,000 IU/mL (approximately 120,000 copies/mL); at week 96, this decreased to six subjects (23.1%) and seven subjects (28%) respectively. Rates of combined response, defined as HBeAg seroconversion, HBV DNA <20,000 IU/mL, and normalization of ALT, were 4/26 (15.4%) in the PEG/Ta1 group and 3/25 (12%) in the PEG group at the end of treatment, and 6/26 (23.1%) in the PEG/Ta1 group and 5/25 (20%) in the PEG group at the end of follow-up (p=0.789). HBsAg data were not discussed in the publication. The authors concluded that the addition of Ta1 was not superior to PEG-IFN-alpha2a alone in HBeAg-positive CHB patients "on the basis of antiviral efficacy." The study's limitations included its small size, OL design, and an HBV DNA cut-off much higher than current standards.

Studies that evaluated Ta1 in combination with NrtIs

Ta1 has been evaluated in combination with NrtIs including famciclovir,[102] lamivudine, and ETV for the treatment of CHB. We did not identify studies that evaluated Ta1 in combination with TAF or TDF. Studies that evaluated Ta1 with NrtIs that are not preferred by professional clinical guidelines (Terrault et al. 2018) are not discussed in detail, as they do not inform the effectiveness of Ta1 with the current preferred treatments.

Wu et al. (2018) evaluated subjects with CHB with compensated cirrhosis who received ETV monotherapy (0.5 mg daily, n=339), or ETV in combination with Ta1 (ETV/Ta1 group, n=351) for 52 weeks in a R, OL study. Subjects received ETV (0.5 mg daily) for 26 weeks before initiating study treatment and continued to receive ETV after the combination phase. The median follow-up period was 38.2 months. The primary endpoint was death, diagnosis of HCC, or liver decompensation. The cumulative incidence of liver decompensation, HCC, or death was similar between the two groups. Per authors, three patients in the ETV group and one in the combination group developed HCC within first 26 weeks. Authors added, "Considering HCC carry-on in

[101] See final guidance for industry entitled, Chronic Hepatitis B Virus Infection: Developing Drugs for Treatment at https://www.fda.gov/media/117977/download.

[102] Famciclovir is a nucleoside analog DNA polymerase inhibitor (See, e.g., label for famciclovir, ANDA 091480, DailyMed, accessed 6/14/2024, https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a5c46194-3692-cd26-0d85-6371974ccc44.) Famciclovir is not found in the 2016 AASLD guidelines (Terrault et al. 2016); 2017 EASL guidelines (EASL 2017); 2018 AASLD guidance (Terrault et al. 2018); 2024 World Health Organization (WHO) guidelines for CHB (WHO 2024); or 2016 APASL guidelines (Sarin et al. 2016).

these patients, we excluded them and recalculated the incidence of HCC. The cumulative incidence of HCC was 3.1% in the ETV group and 3.4% in the ETV/Ta1 group (p=0.913)." During ETV/Ta1 treatment, the HCC incidence was 1.7% versus 2.1% in the ETV monotherapy group; there was a trend toward lower HCC incidence in the ETV/Ta1 group, which authors observed as more evident during the Ta1 add-on period from week 39 to week 78. The proportion of participants achieving undetected HBV DNA was similar in the ETV group (64.6%) and ETV/Ta1 group (69.6%) at week 52, and at week 104 (87.7% and 85.5% respectively). HBsAg clearance rates were similar between the groups; the HBsAg seroconversion rate was 0.3% in both groups at week 52. The virologic response (defined as undetected HBV DNA using an assay with a limit of detection <20 IU/mL, or approximately 120 copies/mL), serologic response, and biochemical response rates were similar between the groups at week 104. Per the authors, there was a trend toward decreased HCC with Ta1 in the combination treatment period, however, statistical significance was not achieved. Per the authors, "[t]he 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." The study limitations included the OL design.

Peng et al. (2020) is a meta-analysis to evaluate the clinical efficacy of ETV administered in combination with Ta1 (ETV/Ta1) versus ETV monotherapy in HBV-related cirrhosis. Seven RCTs involving 1144 subjects were included.[103] Compared with ETV monotherapy, ETV/Ta1 combination therapy led to a higher rate of "complete response," which was not defined in the publication (RR = 1.18; 95% CI, 1.07–1.30). In subjects treated for 24 weeks, the HBV DNA response rate (the HBV DNA cut-off limit used to define a successful response was not provided) and HBeAg loss rate were higher in the ETV/ Ta1 group than in the ETV alone group (RR = 1.91, 95% CI, 1.56–2.35; RR = 2.05, 95% CI, 1.62–2.60 respectively); however, it is unclear from the meta-analysis at what timepoint these data were obtained (i.e., at end of treatment or after a follow-up period). In subjects treated for 48 and 52 weeks, there was no significant difference between ETV/Ta1 and ETV monotherapy in HBV DNA and HBeAg response (RR = 1.07, 95% CI, 0.96–1.18; RR = 1.17, 95% CI, 0.89–1.55 respectively), although it is again unclear when these data were obtained. In the one trial that reported HBsAg loss (Wu et al. 2018), the rate in the ETV/Ta1 group was not significantly different than the ETV alone group (RR = 1.03; 95% CI, 0.15–7.26). The authors concluded that ETV/Ta1 might lead to a higher clinical response in patients with HBV-related cirrhosis, compared to ETV alone; however, the authors noted that the subjects were from China, and so worldwide trials with larger sample sizes are needed to verify the findings. The diagnostic criteria were inconsistent among the included studies, as was disease severity (studies included compensated, decompensated, or unspecified HBV-related cirrhosis). In addition, we were unable to review the primary studies except for Wu et al. 2018, because the publications were either in the Chinese language or could not be located. Our ability to interpret the results of this meta-analysis is also limited by not knowing when the reported outcomes data were obtained relative to treatment.

[103] The authors analyzed data separately for studies that reported complete response (three studies with 270 subjects) and virological response (six studies with 1090 subjects; further divided into subgroups that reported outcomes of treatment for 24 weeks (four studies with 310 subjects) and 48 and 52 weeks (three studies with 780 subjects)). "Virological response" included the rate of undetectable HBV DNA and HBeAg, and HBsAg loss.

Summary of Efficacy Studies

Ta1 has been evaluated as a treatment for CHB as monotherapy and in combination with therapies such as IFNs and NrtIs, such as entecavir. Many studies evaluating Ta1 for CHB were conducted at a time when standard IFN and currently nonpreferred antivirals (e.g., lamivudine), were the available treatment options for CHB. As noted above, these are no longer considered preferred treatments in the treatment guidelines of professional organizations. Studies where Ta1 was evaluated as monotherapy had many limitations, such as small sample sizes, no control groups, lack of blinding, and use of assays with markedly decreased sensitivity compared to assays currently used. The only double-blind study (Mutchnick et al. 1999), which compared Ta1 monotherapy to placebo, failed to demonstrate the efficacy of Ta1 for the treatment of CHB. 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. Studies performed with Ta1 in combination with therapies such as ETV (Wu et al. 2018) and PEG-IFN (Song et al. 2011; Kim et al. 2012) did not demonstrate that Ta1 contributes to efficacy, and the study designs limit our ability to interpret the results. We have limited information regarding the long-term effect of Ta1 on HBV-related clinical outcomes, including cirrhosis, HCC, and death.

b. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

CHB can cause serious health problems, including severe liver damage, cirrhosis, liver cancer, or death.[104]

c. Therapies that have been used for the condition(s) under consideration

There are FDA-approved drug products that treat the same medical condition as that proposed for the Ta1 compounded drug product.[105,106] The following list includes FDA-approved drug products that are antiviral agents (nucleoside and nucleotide analogues) or immunomodulatory agents (i.e., PEG-IFN) indicated for CHB.[107,108] The FDA-approved therapies are available in various formulations/routes of administration:

- Nucleos(t)ide analogues: entecavir, lamivudine, tenofovir alafenamide, adefovir, tenofovir disoproxil fumarate - oral (tablet, solution, powder)
- Inducer of the innate antiviral immune response: peginterferon alfa-2a- SC injection

d. Conclusion

[104] Hepatitis B Basics, CDC website, accessed 5/31/2024, https://www.cdc.gov/hepatitis-b/about/index.html.
[105] FDA considers the existence of FDA-approved or OTC monograph drug products to treat the same condition as that proposed for the nomination relevant to FDA's consideration of the effectiveness criterion, to the extent there may be alternative therapies that have been demonstrated to be effective for certain conditions. See 84 FR 4696.
[106] See Drugs@FDA (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm) or FDA's online label repository (https://labels.fda.gov/) for labels of FDA-approved drug products.
[107] Choosing an Initial HBV Treatment Regimen, accessed 6/3/2024, https://www.hepatitisb.uw.edu/go/hbv/medications-used-to-treat-hbv/core-concept/all.
[108] IFN-alpha products have been discontinued. See: FDA Purple Book, accessed 6/18/2024, https://purplebooksearch.fda.gov/.

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. There have been numerous investigations of Ta1 for the treatment of CHB, many of which are limited by their small size and study design (e.g., lack of control group, outdated therapy in the control arm, lack of blinding, limitations with the choice of efficacy endpoint, and use of assays with markedly decreased sensitivity compared to those recently used for to assess the efficacy of potential therapeutics for CHB). While information from available published studies suggests 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 pegylated interferon or entecavir have demonstrated unclear efficacy, and our ability to interpret them is limited by study design. Although Ta1 has been approved for use in the treatment of HBV infection in other countries, we do not know the current extent of its use. While the 2012 version of the clinical guidelines published by the Asian Pacific Association for the Study of the Liver (APASL) recommended the use of Ta1 as an alternative to IFN or PEG-IFN, the 2016 (most recent) APASL guidelines only acknowledge that Ta1 is an immunomodulatory agent that has been licensed in some Asian countries, and Ta1 is not listed under recommended treatment. Ta1 is not a recommended therapy for CHB in the most current U.S. professional clinical guidelines. In addition, there are currently FDA-approved drugs with established efficacy for the treatment of CHB. The use of Ta1 in lieu of, or causing a delay in, the use of an approved product for treatment of chronic HBV infection could have serious negative sequelae for patients living with chronic HBV infection.

2. Hepatitis C

HCV infection is a liver infection that is primarily transmitted through exposure to infectious blood or body fluids that contain blood.[109] Acute HCV infection (within the first 6 months of HCV exposure) may be asymptomatic or include symptoms such as jaundice, loss of appetite, vomiting, abdominal pain, fever, joint pain, or fatigue. Some patients with acute HCV infection spontaneously clear the virus, while others develop chronic HCV infection (CHC). CHC may cause chronic liver disease and lead to cirrhosis, liver failure, liver cancer, and death.[110]

Treatment is recommended for all people 3 years of age or older with acute or chronic HCV infection.[111,112] The goal of treatment is to achieve virologic cure as evidenced by a sustained virologic response (SVR).[113] SVR is defined as the continued absence of detectable HCV RNA

[109] Clinical Overview of Hepatitis C, CDC website, accessed 5/28/2024, https://www.cdc.gov/hepatitis-c/hcp/clinical-overview/index.html.
[110] Hepatitis C, National Institutes of Health (NIH) National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) website, accessed 5/20/2024, https://www.niddk.nih.gov/health-information/liver-disease/viral-hepatitis/hepatitis-c.
[111] Hepatitis C Basics, CDC website, accessed 5/20/2024, https://www.cdc.gov/hepatitis-c/about/.
[112] See AASLD and Infectious Diseases Society of America (IDSA) HCV Guidance, https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCVGuidance_December_19_2023.pdf.
[113] See AASLD and Infectious Diseases Society of America (IDSA) HCV Guidance, https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCVGuidance_December_19_2023.pdf.

in blood several months (usually 12 weeks) after completing treatment.[114,115] SVR is associated with a >70% reduction in the risk of HCC and a 90% reduction in the risk of liver-related mortality and liver transplantation.[116]

Treatment of HCV infection has evolved substantially in the last few decades. IFN-alpha was used as monotherapy starting in the 1980s, with efficacy "limited to less than 40%" (Manns and Maasoumy 2022). In the 1990s, dual therapy with the nucleoside analogue ribavirin in combination with IFN demonstrated superior efficacy. After modified (long-acting) pegylated interferons (PEG-IFN) showed a favorable PK profile, PEG-IFN administered in combination with ribavirin remained the standard of care from approximately 2001 to 2011, with clinical trials generally demonstrating SVR rates 47-56% for the most common U.S. genotypes (Manns and Maasoumy 2022). Development of direct-acting antiviral agents (DAAs), the first of which were approved in 2011, improved SVR rates and these have become the recommended treatment (Manns and Maasoumy 2022). The likelihood of achieving SVR with DAA therapy among adherent, immunologically competent, treatment-naïve patients with compensated liver disease generally exceeds 95%.[117]

The AASLD and the Infectious Diseases Society of America (IDSA) have developed guidance on testing, managing, and treating HCV infection that is continuously updated.[118] Currently recommended treatment regimens generally involve 8-12 weeks of daily oral DAAs in fixed-dose combination and cure over 95% of patients with few side effects.[119] Example regimens include:[120]

- Glecaprevir (300 mg)/pibrentasvir (120 mg) for 8 weeks
- Sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks

Administration of ribavirin in combination with DAAs is recommended in certain situations.[121] IFN and PEG-IFN are not included in the guidance as a recommended treatment.[122]

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[114] See FDA final guidance for industry entitled, Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment, page 3, at https://www.fda.gov/media/79486/download.
[115] See AASLD and IDSA HCV Guidelines, available at https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCVGuidance_December_19_2023.pdf.
[116] Ibid.
[117] See AASLD and IDSA HCV Guidance, https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCVGuidance_December_19_2023.pdf.
[118] See HCV Guidelines website, accessed 5/13/2024, https://www.hcvguidelines.org/. The guidelines are also available in PDF: AASLD and IDSA HCV Guidelines, https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCVGuidance_December_19_2023.pdf.
[119] Hepatitis C Basics, Centers for Disease Control and Prevention (CDC) website, accessed 5/20/2024, https://www.cdc.gov/hepatitis-c/about/.
[120] Recommended treatment regimens vary depending on factors such as whether a patient is treatment-naïve, presence of cirrhosis (compensated or decompensated), HCV genotype, and previous treatment failures. See AASLD and IDSA HCV Guidelines website, accessed 6/17/2024, https://www.hcvguidelines.org/.
[121] See AASLD and IDSA HCV Guidelines, https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCVGuidance_December_19_2023.pdf.
[122] See AASLD and IDSA HCV Guidelines, https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCVGuidance_December_19_2023.pdf.

FDA issued a guidance for industry to provide recommendations for developing DAAs for treatment of CHC. In the guidance, it is stated that the ability to achieve SVR rates > 90% using only DAAs (with and without ribavirin) in many populations of HCV-infected patients has been well established.[123] The active comparator should be an antiviral drug that is approved and recommended for the treatment of CHC by authoritative scientific bodies based on clinical evidence that also reflects current practice at the time of trial initiation. The recommended primary endpoint is SVR12 (SVR assessed 12 weeks after cessation of treatment).

Ta1 is not mentioned in the AASLD/IDSA treatment guidelines.[124] Other professional organizations such as EASL (EASL 2020) and North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (Leung et al. 2020)) also do not list Ta1 in their treatment guidelines.

a. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

The nomination cited one clinical study evaluating Ta1 for the treatment of CHC (Andreone et al. 1996a), a literature review (Tuthill and King 2013), and information from IPS that discusses the uses of Zadaxin. We also searched published medical literature on Ta1 for the treatment of HCV infection/CHC and retrieved additional publications. The key findings of publications identified in the FDA search and those included in the nomination are summarized below.

Studies which evaluated Ta1 monotherapy

Andreone et al. (1996a) evaluated subjects with CHC who received Ta1 (900 µg/m^2 BSA SC twice weekly) (n=9) or placebo (n=10) for 6 months, with a 6-month follow-up, in a R, DB, PC pilot study. ALT level normalized in one subject treated with Ta1, but the level was "raised" again at the sixth month of follow-up (ALT level was not specified). No subject cleared HCV RNA at the end of therapy or during follow-up.

Studies which evaluated Ta1 in combination with IFNs, with and without ribavirin

Ta1 has been evaluated in combination with IFNs, with and without ribavirin, for the treatment of CHC. As noted above, PEG-IFN has replaced standard IFN; standard IFN-alpha products have been discontinued. In addition, while indications for approved PEG-IFN include CHC, PEG-IFN is not listed in professional guidelines as a recommended treatment for CHC.[125] Therefore, these studies do not help inform the effectiveness of Ta1 in combination with current preferred treatments and are described below only briefly:

Sherman et al. (1998) evaluated subjects with CHC who received IFN-alpha2b (3 MU SC three times per week) (n=37), Ta1 (1.6 mg SC twice weekly) administered in combination with IFN-

[123] See final guidance for industry entitled, Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment (November 2017) at https://www.fda.gov/media/79486/download.
[124] See AASLD and IDSA HCV Guidelines, https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCVGuidance_December_19_2023.pdf.
[125] See AASLD and IDSA HCV Guidelines, https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCVGuidance_December_19_2023.pdf.

alpha2b (3 MU SC three times per week) (n=35), or placebo for both agents (n=37) for 26 weeks in a R, DB, PC trial. At 26 weeks, undetected levels of plasma HCV RNA were seen in 37.1% of IFN/Ta1-treated subjects, 18.9% of IFN-treated subjects, and in 2.7% of those who received placebo. The publication did not include SVR data.

Rasi et al. (1996) evaluated subjects with CHC who received Ta1 (1 mg SC twice weekly) in combination with lymphoblastoid (L)-IFN (3 MU intramuscular (IM) three times per week) (n=15) for 1 year, with a 6-month follow-up, in an OL trial. Subjects received a loading dose of Ta1 (10 mg SC daily for 4 days) at the beginning of the study. Seven subjects (47%) had undetected HCV RNA at 6 months, and 11 (73%) at 1 year. Six months after treatment, six subjects (40%) maintained undetected levels of HCV RNA. Another OL study evaluating IFN-alpha2a (3 MU SC three times per week) in combination with Ta1 (1.6 mg SC twice weekly) (n=12) for 52 weeks observed similar rates of undetected HCV RNA (33% at 24 weeks and 45.5% at 48 weeks) in their preliminary results and noted that SVR would be determined after completion of follow-up (Kullavanijaya et al. 2001).

Moscarella et al. (1998) evaluated IFN-alpha2b (3 MU three times weekly) in combination with Ta1 (1 mg twice weekly) (n=17) versus IFN-alpha2b monotherapy (n=17) for 6 months, with a 12-month follow-up, in a R trial. Eleven subjects (65%) had undetected HCV RNA at 6 months in the IFN/Ta1 group, versus five subjects (29%) in the IFN monotherapy group; the rates of HCV RNA response at 12 months were not provided.

Poo et al. (2008) evaluated Ta1 (1.6 mg SC twice weekly) in combination with PEG-IFN-alpha2a (180 µg SC once per week) and ribavirin (800-1000 mg daily) (n=40) for 48 weeks, with a 24-week follow-up, in an OL trial. Subjects were non-responders to previous IFN-alpha/ribavirin therapy. At 48 weeks (end of treatment), 52.6% of subjects had undetected HCV RNA; at 72 weeks, 21.1% of subjects had undetected HCV RNA. The study limitations included the small sample size, open label design, and lack of a control arm.

Ciancio et al. (2012) also evaluated Ta1 as an add-on treatment to PEG-IFN-alpha2a and ribavirin for CHC in a R, DB, PC trial. Subjects unresponsive to the combination of PEG-IFN-alpha2a or PEG-IFN-alpha2b with ribavirin received PEG-IFN-alpha2a (180 µg per week) with ribavirin (1000-1200 mg daily), plus either Ta1 (1.6 mg SC twice weekly, n=275) or placebo (n=277) for 48 weeks. SVR rates in the intention to treat (ITT) population[126] were similar between the Ta1 (12.7%) and placebo (10.5%) groups. At week 24, 58.6% of subjects in the Ta1 group were non-responders versus 50.9% in the placebo group; treatment was discontinued in subjects who were still HCV RNA positive at week 24. Among subjects who completed all 48 weeks of therapy, the SVR rate was statistically significantly higher in the Ta1 group at 41% (34/83) compared with 26.3% (26/99) in the placebo group ($p = 0.048$). The authors stated that, "the addition of thymosin alpha-1 to the standard of care did not increase the on-treatment HCV viral response." The authors noted that the results raised the speculation that Ta1 may improve the ability to sustain a virologic response and may play a role as a secondary adjuvant for preventing relapses.

[126] The ITT population included all randomized subjects who took at least one dose of study treatment, and also included non-responder subjects (positive HCV PCR after 24 weeks of treatment).

Summary of Efficacy Studies

Ta1 has been evaluated as monotherapy and in combination with IFNs and ribavirin for the treatment of CHC. While study endpoints have varied, including timepoint for SVR assessment, the reported SVR rates ranged from 0-52%. Studies were conducted during a time when IFN or PEG-IFN was a component of the recommended treatment for CHC; as noted above, available therapeutics have evolved substantially, and these treatments are no longer considered standard of care or listed as recommended treatments in the treatment guidelines of professional organizations. The nomination did not include, and our search of the published medical literature did not identify, studies that evaluated Ta1 as compared to, or as an adjuvant therapy with, the current standard of care (i.e., DAAs). Based on the reviewed literature, the efficacy of Ta1 in the treatment of CHC is inferior to the currently available antiviral therapies.

b. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

CHC can be a serious disease resulting in long-term health problems, including liver damage, liver failure, cirrhosis, liver cancer, or death. It is the most common reason for liver transplantation in the United States.[127]

c. Therapies that have been used for the condition(s) under consideration

There are FDA-approved drug products that treat the same medical condition as that proposed for the Ta1 compounded drug product. The following list includes currently available FDA-approved drug products indicated for CHC:

- Direct-acting antiviral therapies (DAAs): oral (tablet, pellets) - interfere directly and specifically with certain viral proteins required for HCV replication, such as nonstructural proteins (NS)3/4A protease inhibitor (PI) and NS5A inhibitor (Manns and Maasoumy 2022). Currently approved DAAs include:[128]

    - Fixed-dose combinations:
        - Elbasvir (HCV NS5A inhibitor) and grazoprevir (HCV NS3/4A PI)
        - Glecaprevir (HCV NS3/4A PI) and pibrentasvir (HCV NS5A inhibitor)
        - Ledipasvir (HCV NS5A inhibitor) and sofosbuvir (HCV nucleotide analog NS5B polymerase inhibitor)
        - Sofosbuvir and velpatasvir (HCV NS5A inhibitor)
        - Sofosbuvir, velpatasvir, and voxilaprevir (HCV NS3/4A PI)

    - Single ingredient:
        - Sofosbuvir

[127] Hepatitis C Basics, CDC website, accessed 5/21/2024, https://www.cdc.gov/hepatitis-c/about.
[128] Individual drug product labels provide further information, e.g., if a DAA drug product is indicated for use in a specific HCV genotype. Please see the drug product labels for further information.

- Nucleoside analog: ribavirin[129] - oral (capsules, tablets)
- Inducer of the innate antiviral immune response: peginterferon alfa-2a - SC injection

d. Conclusion

Based on available clinical information, there are insufficient data to establish the effectiveness of Ta1 for the treatment of HCV infection, which has the potential to be a serious and life-threatening condition. Available clinical studies were small, often single-arm and/or open label studies that were conducted with therapies such as interferon and pegylated interferon (with or without ribavirin) that are no longer recommended in the treatment guidelines of clinical professional organizations for the treatment of CHC. These older therapies achieved a wide range of SVR rates that were all markedly lower than the SVR rates observed in association with currently recommended oral HCV DAA drug combination therapies. Achieving SVR is considered a virologic cure of CHC; patients achieving SVR experience reduction in the risk of development of HCC, liver-related mortality, and liver transplantation. Therefore, treating patients with Ta1, which has not been associated with a high rate of SVR, when there are available FDA-approved therapies that have been shown to be highly effective, could have serious negative implications for patients. There is no information available to evaluate whether Ta1 in combination with current standard of care therapy provides any advantage over the standard of care alone. FDA lacks the information necessary to make a conclusion about the potential benefit of Ta1 for treatment of acute or chronic HCV infection. In addition, there are currently FDA-approved drugs with established efficacy for the treatment of HCV infection.

3. Human immunodeficiency virus (HIV)

Human immunodeficiency virus type 1 (HIV-1; hereafter referred to as "HIV") is a virus that attacks the body's immune system and results in chronic infection.[130] The key component of the immune deficiency associated with HIV is a marked reduction in cluster of differentiation 4 (CD4) positive T-cells and derangements in other immunologic parameters. If untreated, HIV infection may progress to acquired immunodeficiency syndrome (AIDS), the most advanced stage of infection, defined as the presence of HIV infection with a $CD4^+$ T cell count fewer than 200 cells/cubic millimeter $(mm)^3$ and/or the presence of one or more AIDS-defining clinical condition/s, including opportunistic infections, malignancies and other clinical syndromes.[131]

The HIV treatment guidelines of the Department of Health and Human Services (DHHS)[132] do not mention Ta1 as a treatment option. Current treatment guidelines recommend initiating

[129] Of note, currently approved ribavirin drug products are indicated for use in combination with IFN alfa-2b (pegylated and non-PEGylated) for the treatment of CHC in patients 3 years of age or older with compensated liver disease. Professional guidelines do not list IFN as a currently recommended treatment for CHC, but suggest that ribavirin be administered with DAAs in certain situations (See: AASLD and IDSA HCV Guidelines, https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCVGuidance_December_19_2023.pdf).
[130] Available at https://www.who.int/news-room/fact-sheets/detail/hiv-aids. Accessed July 2, 2024.
[131] Available at https://www.fda.gov/files/drugs/published/Human-Immunodeficiency-Virus-1-Infection--Developing-Antiretroviral-Drugs-for-Treatment.pdf. Accessed July 2, 2024.
[132] Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. Accessed July 2, 2024.

antiretroviral therapy (ART) as soon as possible after diagnosis to reduce HIV-related morbidity and mortality and the risk of transmission (Goldschmidt and Chu 2021, Kwong 2020). The goal of antiretroviral treatment is to indefinitely maintain suppression of HIV replication. In practice, HIV replication is monitored by measuring plasma HIV RNA, colloquially referred to as viral load. The goal of ART is to reduce the viral load to an undetectable level, which is the level at which plasma HIV RNA is too low to be detected by a sensitive assay.[133] More than 30 unique antiretroviral drugs (ARVs) have been approved by the FDA which can be combined in a regimen tailored to each individual (Refer to Section II.D.3.c). Based on the mechanism of action, there are nine classes of ARVs approved by the FDA for the treatment of HIV[134] which are outlined below. Of note, there is no FDA-approved immune-targeting therapy.

- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Nucleos(t)ide reverse transcriptase inhibitors (NRTIs)
- Protease inhibitors (PIs)
- Integrase strand transfer inhibitors (INSTIs)
- gp41-directed fusion inhibitors
- CCR5 co-receptor antagonists
- gp120-directed attachment inhibitors
- CD4-directed post-attachment inhibitors
- Capsid inhibitors

The selection of ARVs in these regimens depends on the patient's comorbidities, disease stage, the genetic makeup of their virus and prior treatment history, potential side effects, and possible interactions with the patient's concomitant medications.[135] A decrease in viral load following initiation of ART is associated with a reduced risk of progression to AIDS or death. Based on several analyses of data from multiple HIV clinical trials, the FDA Antiviral Drug Advisory Committee concluded that treatment-induced decreases in HIV viral load were highly predictive of meaningful clinical benefit and that HIV viral load measurements could serve as endpoints in trials designed to support drug approvals.[136] Therefore, HIV viral load is a validated and clinically meaningful surrogate for predicting the efficacy of ARVs. The committee also recommended that changes in $CD4^+$ T cell counts be consistent with observed viral load changes when considering approval of an ARV. At the present, the primary endpoint in HIV treatment trials is based on sustained HIV viral load suppression, while $CD4^+$ T cell count-based parameters are included as secondary endpoints.[137] The goal of treatment is sustained virologic suppression, defined as confirmed plasma HIV RNA persistently below the limit of detection, which may vary by assay (generally <20 copies/mL). An undetectable viral load is typically achieved within 8-24 weeks depending on pretreatment viral load and ART regimen selected. Patients who fail to achieve sustained virologic suppression by 24 weeks are reassessed for adherence, ART drug absorption, viral resistance, and drug interactions.

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[133] Available at https://hivinfo.nih.gov/understanding-hiv/fact-sheets/hiv-treatment-basics. Accessed July 2, 2024.
[134] Available at https://hivinfo.nih.gov/understanding-hiv/fact-sheets/fda-approved-hiv-medicines.. Accessed July 2, 2024.
[135] Available at https://www.ajmc.com/view/hivaids-diagnosis-and-treatment-guidelines. Accessed July 2, 2024.
[136] Available at https://www.fda.gov/media/86284/download. Accessed July 2, 2024.
[137] Available at https://www.fda.gov/files/drugs/published/Human-Immunodeficiency-Virus-1-Infection--Developing-Antiretroviral-Drugs-for-Treatment.pdf. Accessed July 2, 2024.

In clinical practice, the clinical status of patients while on ART is monitored by measuring the HIV viral load and $CD4^+$ T cell counts (Goldschmidt and Chu 2021). The $CD4^+$ T cell count is the most important laboratory indicator of immune function. Multiple sources of variability in $CD4^+$ cell count have been reported, including variability secondary to physiologic factors and in intra-laboratory measurements. As such, a significant change is approximately 30% change in the absolute count or a 3% change in $CD4^+$ T cell proportion (the proportion of white blood cells or lymphocytes that are $CD4^+$ T cells) (Raboud et al. 1995; Malone et al. 1990). Monitoring lymphocyte subsets other than $CD4^+$ T cells has not proven clinically useful, therefore, monitoring of lymphocyte subsets other than $CD4^+$ T cells is not recommended by the guidelines for the use of antiretroviral agents in adults and adolescents with HIV published by the DHHS.[138]

a. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

We identified five published studies of Ta1 in subjects with HIV.

Schulof et al. (1986): This phase 1/2 trial evaluated the safety, long-term tolerance, and immunomodulatory effects of thymosin fraction five (TF5)[139] and Ta1 in 42 human T-helper cell lymphotropic retrovirus (HTLV-III), later renamed HIV-1, seropositive subjects. The subjects were men who have sex with men (MSM) and/or hemophiliacs with low absolute T4 cell (i.e., $CD4^+$ T cell) numbers ($<557/mm^3$). Groups of 10 subjects each were treated with one of three doses of TF5 (30, 60, and 120 mg) or a single dose of Ta1 600 µg by daily subcutaneous administration for 10 weeks, followed by twice weekly for 4 weeks. Two additional subjects were treated with TF5 120 mg to replace two others who had discontinued therapy shortly after the treatment due to severe local skin reactions. Of the four treatments, marked immunomodulatory effects on T-cell function (mean T-cell lymphoproliferative responses to alloantigens (MLR) and interleukin-2 (IL-2) production), were only seen with TF5 60 mg; TF5 60 mg improved the mean MLR in six subjects, but the MLR returned to baseline in four of them after switching to twice weekly injection. Mean mitogen-induced IL-2 production was transiently restored to the levels of uninfected control donors.[140] None of the treatments affected absolute $CD4^+$ T cell numbers, natural killer (NK) cell activity, HTLV-III antibody titer or the expression of several surrogate markers of AIDS. At the time of the study, a methodology for accurately quantifying viral load had not been developed, and viral load had not been established as a surrogate marker of efficacy. No subjects treated with Ta1 developed AIDS; however, follow-up was only 5-7 months and there was no control group for comparison. The authors concluded that thymosin exerted an immunorestorative effect only in subjects receiving TF5 60 mg, in whom transient improvements in T-cell function were observed. The authors also concluded that Ta1 appeared to be ineffective in these subjects.

[138] Available at https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/plasma-hiv-1-rna-cd4-monitoring?view=full. Accessed July 2, 2024.
[139] Thymosin fraction five (TF5) is a partially purified calf thymus preparation (Schulof et al. 1986). TF5 contains at least 40 peptide components.
[140] The control donors were consisted of healthy, heterosexual male hospital personnel of similar age to the study subjects.

We note that this is the only study that explored the effects of Ta1 monotherapy. However, no conclusions about clinical benefit can be reached because the effect on plasma HIV RNA, the validated surrogate endpoint, was not evaluated, there was no effect on the $CD4^+$ T cell count, and the limited duration of follow-up precluded assessment of effects on clinical endpoints such as AIDS-defining illness or death. Further, the immune parameters evaluated, namely, the mean T-cell lymphoproliferative responses to alloantigens and IL-2 production, are not validated or reasonably likely surrogate endpoints; and the clinical meaningfulness of changes in these parameters is unknown.

Garaci et al. (1994): This randomized, non-blinded clinical study examined the effects of ART (zidovudine) and combined immunotherapy (Ta1 and interferon-alpha) for 1 year in 28 subjects with HIV who had $CD4^+$ T cell counts of 200 - 500/mm^3. Subjects were randomly assigned to four groups (seven subjects per group); the first group received 500 mg/day zidovudine (AZT), the second group received AZT plus 2 MU IFN-alpha intramuscularly twice weekly, the third group received AZT plus 1 mg Ta1 subcutaneously twice weekly, and the fourth group received AZT plus Ta1 plus IFN-alpha. After 18 months, 23 subjects remained in the study. In the AZT group, the mean $CD4^+$ T cell count was 382±61 before treatment and 331±63 after 12 months. In the group receiving AZT and IFN-alpha, the $CD4^+$ T cell counts changed from 396±98 to 392±140, and in the group receiving AZT and Ta1, the $CD4^+$ T cell counts changed from 411±84 to 446±115. There were no significant differences in $CD4^+$ T cell counts in these groups. However, the group treated with AZT, Ta1 and IFN-alpha showed a $CD4^+$ T cell counts of 309±77 before treatment and 496±230 after 12 months, which persisted up to 18 months (583±216 at 12 months to 633±281 at 18 months). The proportion of $CD4^+$ T cells with viral DNA was significantly, albeit modestly, lower (circa twofold) ($p = 0.013$) in subjects receiving three drugs compared to those who received only AZT. The clinical significance of this difference is unclear. The authors concluded that combination immunotherapy exerts a long-term beneficial effect as indicated by an increased $CD4^+$ T cell counts even after 18 months of treatment. However, 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.

Ramachandran et al. (1996): This single-arm, OL study evaluated the synergistic antiviral effects of polyethylene glycolated interleukin-2 (PEG-IL-2) and Ta1 in addition to zidovudine in 12 HIV-infected subjects whose $CD4^+$ T cell counts were 50-250 cells/mm^3. The subjects took zidovudine 600 mg/day in divided doses at least 8 weeks before study initiation and continued throughout the study period. PEG-IL-2 at 10^6 IU/m^2 was administered by bolus infusion over 30 minutes every other week for 20 weeks. After four infusions of PEG-IL-2, at week 8, Ta1 at a dose of 0.4 μg/m^2 was given subcutaneously twice a week. At week 12, the Ta1 dose was increased to 1600 μg/m^2 and was continued with PEG-IL-2 for an additional 8 weeks. The study showed an increased number of $CD4^+$ T cell counts in all subjects after PEG-IL-2 administration, followed by a rapid decline to baseline when PEG-IL-2 was not given. The addition of Ta1 did not further increase the $CD4^+$ T cell count observed. There were also no significant mean lymphocytic proliferative responses to tetanus toxoid, *Candida* antigen, and HIV antigens. Virologic monitoring showed no evidence of increased HIV replication. The authors concluded that PEG-IL-2 affected the $CD4^+$ T cell count but the effect of Ta1 was unclear.

Chadwick et al. 2003: This phase 2 RCT evaluated the effectiveness of Ta1 in stimulating immune reconstitution in combination with highly active antiretroviral therapy (HAART). Twenty HIV-infected subjects with viral loads <400 copies/mL and $CD4^+$ T cell counts less than 200 cells/μL were randomized to receive 6.4 mg Ta1 via subcutaneous injection weekly in two divided doses (3.2 mg Ta1 subcutaneous injections twice weekly) or controls who received no injections for 12 weeks. Subjects continued their usual antiretroviral therapy throughout the study period. The primary endpoint was the change in $CD4^+$ T cell count from baseline to week 12. Secondary endpoints were the change in $CD8^+$ T cell count at week 12, the change in $CD4^+$ T cell count at weeks 4 and 8, the change in CD45[141] RO^+ and RA^+ in $CD8^+$ and $CD4^+$ T cells at weeks 4, 8 and 12, and the change in PBMC signal joint T cell receptor rearrangement excision circles (sjTREC). The $CD4^+$ and $CD8^+$ T cell counts showed upward trends in both groups over 12 weeks but there was no significant difference between the Ta1 and control groups. Viral load increased to detectable levels (>400 copies/ml) in three subjects at week 12. However, there was a significant increase in mean sjTREC levels in the Ta1 group at week 12 compared to controls (+27.9 Ta1 vs -3.9 control group; p =0.035). The authors concluded that Ta1 was not effective in inducing a substantial rise in $CD4^+$ T cell counts and the increase in sjTREC in the Ta1 group reflected an increase in naïve lymphocytes, which are recent thymic emigrants. The study, however, did not observe an increase in the naïve T cell counts, possibly due to rapid acquisition of a memory phenotype by naïve cells. The authors suggested further studies with longer treatment durations and populations with higher initial $CD4^+$ T cell counts to assess augmentation of the immune response to HAART.

Chen et al. (2024): This 24 week, single-arm, OL study evaluated the effectiveness of Ta1 in reconstituting the immune response in 20 HIV infected immunological non-responders (INR)[142] with viral suppression (HIV RNA <50 copies/mL) for at least 2 years following ART and $CD4^+$ T cell counts of 100 - 350 cells/μL. In the first 2 weeks, each subject received a daily subcutaneous injection of 1.6 mg Ta1, followed by twice weekly injections for the next 22 weeks. Subjects continued their ART regimens throughout the study period. The primary endpoint was the change in $CD4^+$ T cell count and $CD4^+/CD8^+$ T cell ratio from baseline to week 24. The secondary endpoints were changes in T cell counts and subsets, proportions of immune exhausted T cells expressed as programmed cell death 1 (PD-1) and T cell immunoglobulin and mucin domain-containing molecule-3 (TIM-3) and PBMC sjTREC at each visit. The $CD4^+$ T cell count gradually but non-significantly increased throughout the treatment period, but the $CD4^+/CD8^+$ T cell ratio was unchanged. Thymic output, measured by the level of PBMC sjTREC, increased non-significantly at week 24 compared to baseline. However, Ta1 significantly increased the naïve $CD4^+$ and $CD8^+$ T cell proportion at 24 weeks compared to baseline (17.2% vs 41.1%, p <0.001; 13.8% vs 26.6, p=0.008). The proportions of $CD4^+$ T cells and $CD8^+$ T cells expressing PD-1 significantly decreased ($CD4^+PD\text{-}1^+$, 14.1% vs. 6.5%, p=0.002; $CD8^+PD\text{-}1^+$, 8.5% vs 4.1%, p<0.001). The proportions of $CD4^+$ T cells and $CD8^+$ T cells expressing TIM-3 decreased non-significantly. HIV viral load was stable and below the

[141] CD45 is expressed on all T lymphocytes, which may be divided into a subset expressing the high molecular weight isoform containing the A exon (CD45RA) and a subset expressing lower molecular weight isoforms, including CD45RO. CD45RA is expressed on naïve T cells and CD45RO is expressed on T cells that have encountered antigens (Helbert et al. 1997)

[142] Immunological non-responders are mainly characterized by impaired $CD4^+$ T cell restoration, but the functions of many other immune cells could also be reduced regardless of ART treatment with increased risk or morbidity and mortality compared with those patients that reconstitute their immunity under treatment (Matteucci et al. 2017).

minimum detection level. The authors concluded that Ta1 tended to improve $CD4^+$ T cell counts and thymic output, albeit non-significantly. The limitations of the study included the small sample sizes, lack of control group, and short treatment duration.

Summary of Efficacy Studies

None of the studies demonstrated efficacy based on the regulatory measures of clinical benefit or decrease in viral load. Furthermore, four out of five studies showed no benefit of Ta1 in the treatment of HIV. Only Garaci et al. (1994) reported that Ta1, combined with IFN-alpha and zidovudine significantly increased the $CD4^+$ T cell count, which is not a surrogate marker for clinical treatment outcomes. However, the contribution of Ta1 to the immunomodulatory effect when combined with AZT and IFN-alpha limits our ability to interpret these data. In contrast, the other four clinical studies did not consistently demonstrate an effect on $CD4^+$ T cell count.

b. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

HIV infection is a serious and life-threatening disease; HIV attacks the body's immune system by destroying $CD4^+$ T cells, resulting in susceptibility to opportunistic infections and infection-related cancers.[143] Without treatment with a combination of FDA-approved drugs, as recommended by the DHHS HIV treatment guidelines, infection with HIV progresses to AIDS and death secondary to opportunistic infections and cancers.

c. Therapies that have been used for the condition(s) under consideration

There are FDA-approved drug products that treat the same medical condition as FDA has evaluated for the proposed compounded drug product containing Ta1-related BDSs. The following list includes currently available FDA-approved drug products indicated for HIV,[144] which are available as individual ARV drugs and as combinations of two or more drugs (fixed-dose combination drugs):

- NRTIs (e.g., abacavir)
- NNRTIs (e.g., doravirine)
- protease inhibitors (e.g., atazanavir)
- gp41 directed fusion inhibitors (e.g., enfuvirtide)
- integrase strand transfer inhibitors (e.g., dolutegravir)
- CCR5 co-receptor antagonists (e.g., maraviroc)
- gp120-directed attachment inhibitors (e.g., fostemsavir)
- post-attachment inhibitors (e.g., ibalizumab-uiyk)
- capsid inhibitors (e.g., lenacapavir).

d. Conclusion

[143] Available at https://www.ajmc.com/view/hivaids-diagnosis-and-treatment-guidelines. Accessed July 2, 2024.
[144] https://www.fda.gov/consumers/free-publications-women/hiv-and-aids-medicines-help-you#nucleo. Accessed June 11, 2024.

There is insufficient evidence to conclude that Ta1 is effective for the treatment of HIV infection. The findings from five published clinical studies of Ta1 in subjects with HIV infection are inconclusive because the studies were not adequately designed to evaluate clinically meaningful effects of Ta1. 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. An effect on $CD4^+$ T cell count alone is not a validated or a reasonably likely surrogate endpoint for HIV treatment trials. Further, an increase in $CD4^+$ T cell count was not consistently observed in the studies, and available information suggests that it is uncertain whether Ta1 can reliably achieve a durable increase in $CD4^+$ T cell counts or that such an increase is clinically meaningful. In addition, changes in the laboratory-based immune parameters that were evaluated in these studies, for example, T-cell lymphoproliferative response to alloantigens and PBMC sjTREC, have not been shown to correlate with clinical response to HIV therapy and, importantly, these are not validated surrogate endpoints. Other major limitations with the published studies include inadequate sample size to demonstrate effects on the validated endpoints, the use of unapproved products and non-preferred concomitant therapies (IFN and zidovudine, respectively) in the control arm, lack of randomization and/or blinding, and limited duration of follow-up for an assessment of the therapeutic response durability.

FDA concludes that there is insufficient evidence to support the efficacy of Ta1 for the treatment of HIV infection. There are numerous FDA-approved drug products for the treatment of HIV. As HIV is a serious and life-threatening disease for which there are available FDA-approved therapies and because there is no compelling evidence of a clinical benefit of Ta1, we recommend that Ta1 not be added to the list of substances that can be used in compounding for the treatment of HIV infection.

4. Coronavirus disease (COVID-19)

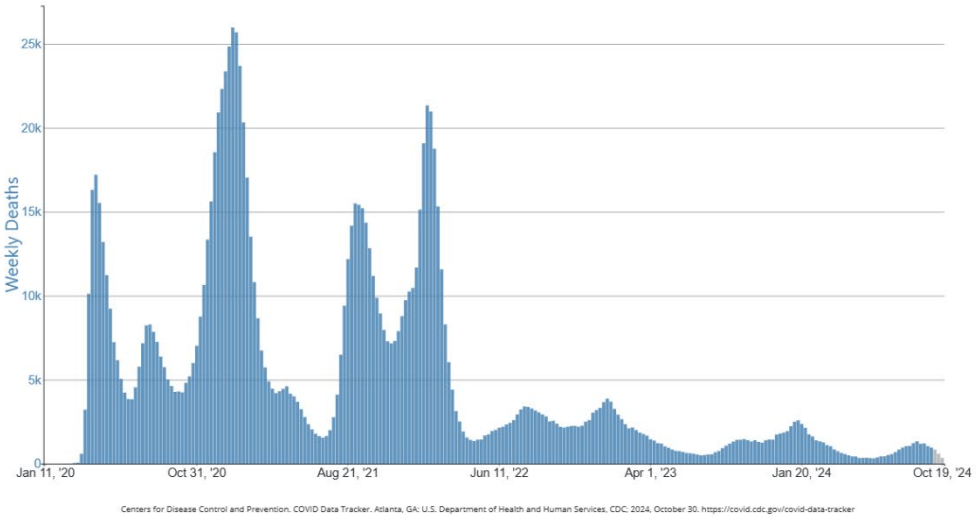
COVID-19 is the disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which emerged in December 2019 and caused a pandemic.[145] Two main processes are thought to drive the pathogenesis of COVID-19. Early in the clinical course, the disease is primarily driven by the replication of SARS-CoV-2. Later in the clinical course, the disease is driven by a dysregulated immune/inflammatory response to SARS-CoV-2 infection, which may lead to further tissue damage and thrombosis. Therefore, therapies that directly target SARS-CoV-2 are anticipated to have the greatest effect early in the course of the disease, whereas immunosuppressive, anti-inflammatory, and antithrombotic therapies are likely to be more beneficial after COVID-19 has progressed to stages characterized by hypoxemia, endothelial dysfunction, and immunothrombosis.[146] Viruses are constantly changing, including SARS-CoV-2, the virus that causes COVID-19. These changes occur over time and can lead to new variants of the SARS-CoV-2 virus.[147] Some changes may affect the virus's properties, such as how

[145] https://www.hopkinsmedicine.org/health/conditions-and-diseases/coronavirus. Accessed October 8, 2024.
[146] https://wayback.archive-it.org/4887/20240626155414/https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf. Accessed October 8, 2024.
[147] https://www.cdc.gov/covid/about/?CDC_AAref_Val=https://www.cdc.gov/coronavirus/2019-ncov/your-health/about-covid-19.html. Accessed June 6, 2024.

easily it spreads, the associated disease severity, or the performance of vaccines, therapeutic medicines, diagnostic tools, or other public health and social measures.[148]

Currently, most people in the United States have some degree of immunity to SARS-CoV-2 due to COVID-19 vaccination or SARS-CoV-2 infection. The increase in population immunity and the change in variants have led to a decrease in the rate of severe disease caused by COVID-19.[149] Figure 8[150] shows the number of deaths per week since the start of the pandemic.

Figure 8. Provisional COVID-19 Deaths, by Week, in The United States, Reported to CDC.



Publications discussing Ta1 use in subjects with COVID-19 were published from 2020 to 2024. Articles published prior to 2022 do not take into account data about the more recent variants, which are responsible for current infections, or newer treatment modalities.

The nomination did not include, and FDA was not able to find articles that discussed the use of Ta1 in children with COVID-19 or in adults with COVID-19 in the outpatient setting. This section will focus on the use of Ta1 in the care of adults with acute COVID-19 in the hospital setting.

Treatment guidelines for adults hospitalized with acute COVID-19 infection published by the United States National Institute of Health (NIH) and the World Health Organization (WHO) categorize recommended interventions based on disease severity. The NIH classifies recommendations based on the following 5 categories[151]:

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[148] https://www.who.int/activities/tracking-SARS-CoV-2-variants . Accessed June 6, 2024.
[149] https://wayback.archive-it.org/4887/20240626155414/https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf. Accessed October 8, 2024.
[150] https://covid.cdc.gov/covid-data-tracker/#trends_weeklydeaths_select_00. Accessed June 6, 2024.
[151] https://wayback.archive-it.org/4887/20240626155414/https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf. Accessed October 8, 2024.

1. Hospitalized for reasons other than COVID-19
2. Hospitalized but does not require supplemental oxygen
3. Hospitalized and requires conventional oxygen
4. Hospitalized and requires high flow nasal canula (HFNC) or non-invasive ventilation (NIV)
5. Hospitalized and requires mechanical ventilation (MV) or extracorporeal membrane oxygenation (ECMO)

WHO definitions of disease severity for COVID-19 are as follows[152]:

- Critical COVID-19 – Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.
- Severe COVID-19 – Defined by any of:
    - Oxygen saturation, SpO2< 90% on room air
    - Signs of pneumonia
    - Signs of severe respiratory distress (in adults, accessory muscle use, inability to complete full sentences, respiratory rate > 30 breaths per minute; and, in children, very severe chest wall in-drawing, grunting, central cyanosis, or presence of any other general danger signs including inability to breastfeed or drink, lethargy, convulsions or reduced level of consciousness).
- Non-severe COVID-19 – Defined as the absence of any criteria for severe or critical COVID-19.

Neither the NIH nor the WHO guidelines discuss the use of Ta1 for treatment of COVID-19. Endpoints for effectiveness of therapies for COVID-19 have included time to recovery within 29 days after starting an intervention, clinical status based on a rating scale[153] at day 15 following an intervention, all-cause mortality by day 29 after an intervention, time to progression to MV or death through day 28, time from randomization to discharge or death up to day 28.

a. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

The nomination did not include references to support the use of Ta1 for COVID-19. The references discussed below were found by FDA.

Shehadeh et al. 2022: Although this study is discussed in several of the meta-analyses described below, it is one of only two RCTs and is the only trial completed in the United States; it is

[152] Therapeutics and COVID-19: living guideline, 10 November 2023. Geneva: World Health Organization; 2023.
[153] 8-point ordinal scale (OS) consisting of the following categories: 1. Not hospitalized, no limitations on activities [OS-1]; 2. Not hospitalized, limitation on activities and/or requiring home oxygen [OS-2]; 3. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care [OS-3]; 4. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise) [OS 4]; 5. Hospitalized, requiring supplemental oxygen [OS 5]; 6. Hospitalized, on non-invasive ventilation or high-flow oxygen devices [OS 6]; 7. Hospitalized, on invasive mechanical ventilation or ECMO [OS 7]; and 8. Death [OS 8] (from baricitinib label https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/207924s007lbl.pdf). Accessed on June 6, 2024.

therefore discussed in detail here. In this OL, prospective trial, 49 hospitalized adults with COVID-19, lymphocytopenia, and hypoxemia were randomized to receive either 1.6 mg of Ta1 via the SC ROA daily for seven days in addition to the current standard of care for COVID-19 treatment (n=23) or standard of care treatment only (n=26). Exclusion criteria included use of invasive mechanical ventilation (IMV), multiorgan failure, advanced cancer being treated with cytotoxic chemotherapy, history of solid organ or bone marrow transplantation, and use of hydroxychloroquine or other immunomodulatory medications not included in standard of care treatments.

Concomitant medications used by study subjects included remdesivir, corticosteroids, baricitinib, and tocilizumab. Subjects were recruited beginning in September 2020. The primary endpoint was time to clinical recovery (defined as the length of time for a subject to no longer require supplemental oxygen support or to improve SpO2 to >93% without supplemental oxygen). Secondary endpoints were 28-day all-cause mortality and use of IMV. There were no differences between treatment groups for the primary or secondary outcomes. Limitations of this study were the small sample size and open label design.

Shetty et al. 2022: Although this study is discussed in several of the meta-analyses described below, it is one of only two RCTs and is therefore discussed in detail here. In this DB prospective trial conducted in India, 105 hospitalized adults with moderate (n=65) or severe (n=40) COVID-19 were randomized to receive either a placebo or 1.6 mg of Ta1 via the SC ROA either two (moderate group) or three (severe group) times a day for 7 days as an adjuvant to standard of care. Concomitant medications used by the subjects included steroids, antivirals, and other disease-modulating drugs such as hydrochloroquine or tocilizumab. The primary endpoint was 28-day all-cause mortality. In the moderate group, 48 subjects received Ta1 and 17 subjects received placebo. In the severe group, 27 subjects received Ta1 and 13 subjects received placebo. Moderate COVID-19 was defined as respiratory rate ≥ 24 breaths/min; SpO2, from >90 to 94% on room air. Severe COVID-19 was defined as respiratory distress with respiratory rate ≥ 30 breath/min; SpO2 ≤ 90% on room air; arterial blood oxygen partial pressure (PaO2)/fraction of inspired oxygen (FiO2) ≤ 200 mm Hg (1 mm Hg 0.133 kPa); or subject presented with respiratory failure requiring mechanical ventilation support. The authors report that Ta1 was associated with a reduction in mortality vs placebo in the severe group. For secondary outcomes, the authors report a decrease in WHO ordinal scale in the Ta1 arm vs placebo for both moderate and severe groups, fewer ventilator days in the Ta1 group, and improved SpO2 levels in the Ta1 arm for both severe and moderate groups. They reported fewer median number of days of hospitalization in the moderate Ta1 group compared to placebo.

Limitations of this study include its small sample size, and the fact that the authors do not specify when the data was collected. Dates of data collection would be important in understanding the current circulating viral strain at the time of the study as well as other available treatments. It is unclear when in the course of the illness subjects began intervention (on admission to hospital, or after certain length of time) and how this may have impacted the treatment outcomes. It is unclear how comorbidities and concomitant medications were distributed among the treatment groups and outcomes. The authors did not state the numerical mortality outcomes for the moderate group or the study group as a whole; results were only provided for the severe group. The mortality outcomes for the severe group were stated as a percentage and in a graph, but not

as actual numbers of subjects. Based on the reported percentages and number of enrolled subjects, the actual number of subjects who died in the severe group vs. the number of subjects who died in the placebo group are small (three vs. five deaths respectively).

Four meta-analyses were found, and Table 4. lists the articles considered in each meta-analysis.

Table 4. Summary of References Included in Meta-Analyses.

Meta-analysis Title	Liu et al. 2022	Shang et. al 2023	Wang et al. 2023	Soeroto et al. 2023
Included References				Li et al. 2021
	Wu et al. 2020	Wu et al. 2020	Wu et al. 2020	Wu et al. 2020
	Wang et al. 2021	Wang et al. 2021	Wang et al. 2021	
	Liu et al. 2020	Liu et al. 2020	Liu et al. 2020	Liu et al. 2020
		Huang et al. 2021	Huang et al. 2021	
		Liu et al. 2021	Liu et al. 2021	Liu et al. 2021
	Sun et al. 2021	Sun et al. 2021	Sun et al. 2021	Sun et al. 2021
		Wang et al. 2022*	Wang et al. 2022*	
		Shetty et al. 2022	Shetty et al. 2022	Shetty et al. 2022
		Shehadeh et al. 2022	Shehadeh et al. 2022	Shehadeh et al. 2022
				Mustafa et al. 2022

*The full text of this article is written in Chinese with an abstract written in English

Liu et al. 2022: In this meta-analysis, the authors included four retrospective cohort studies conducted early in the pandemic. Subjects were hospitalized adults with COVID-19. The authors state that the meta-analysis showed that there was no association between Ta1 treatment and mortality. Limitations of this meta-analysis are that it includes a small number of studies, the data was collected early in the pandemic, and it is unclear if the outcomes would be reproducible given the current circulating strain and changes in treatments since the study was completed.

Shang et al. 2023: In this meta-analysis, the authors included nine studies (including Shehadeh et al. 2022 and Shetty et al. 2022 that were discussed above). The other seven studies were retrospective cohort studies and included all the studies from the meta-analysis by Liu et al. 2022. The authors state that the meta-analysis results indicated Ta1 therapy had no statistically significant effect on mortality and that the results do not support the use of Ta1 in hospitalized adult patients with COVID-19. In the subgroup analyses that examined Ta1's effect on mortality based on age, sex, and disease severity, the sample sizes were small, and the individual studies were not designed to answer these questions. These could be hypothesis generating observations, but without confirmation in a larger RCT, it is unclear whether Ta1 would be effective in certain subgroups. There is heterogeneity between studies in the definition of disease severity, concomitant treatments, and dose and frequency of exposure to Ta1 (in some studies the dose and frequency was not reported), making it difficult to compare the study outcomes. It is also noted that although the meta-analysis lists certain doses of Ta1 received by

subjects in some of the retrospective cohort studies, the studies themselves do not list these doses so it is unclear how this information was obtained.

Wang et al. 2023: This meta-analysis included the same nine studies that were evaluated in Shang et al. 2023. The authors state that no differences were found in mortality or length of hospitalization between subjects who did and did not receive Ta1. This conclusion concurs with the conclusions of the meta-analyses by Liu et al. 2022 and Shang et al. 2023. The authors of this meta-analysis conducted subgroup analyses based on some but not all of the references to evaluate outcomes for mortality and hospital length of stay based on severity of disease (serious vs. non-serious). They report that there appeared to be a mortality benefit for those who received Ta1 in the serious group and there appeared to be a reduced length of hospital stay for those in the non-serious group who received Ta1. A limitation of this study is that the authors do not specify how they define severity of disease and whether this definition differed between the studies. Two studies had no data on disease severity. Additionally, the conclusions about length of stay were made based on data from four of the studies. Because the majority of these studies were conducted early in the pandemic, it is unclear if the results would be reproducible in patients hospitalized with the current circulating strain of COVID-19 and who have access to therapies that were not available at the time most of these studies were conducted. Additionally, there is heterogeneity between studies in the definition of disease severity, concomitant treatments, and dose and frequency of exposure to Ta1 (in some studies the dose and frequency was not reported), making it difficult to compare the study outcomes.

Soeroto et al. 2023: This meta-analysis of eight studies included some of the studies evaluated in the other three meta-analyses, but also included two additional retrospective cohort studies (Li et al. 2021 and Mustafa et al. 2022). The authors of the meta-analysis reported that they evaluated mortality, need for mechanical ventilation and hospital length of stay as endpoints in adults hospitalized with COVID-19 who received either standard of care or standard of care and Ta1. Mixed results were reported by the authors who stated that use of Ta1 was associated with a lower mortality rate, but that data from six studies showed that treatment with Ta1 did not reduce the need for mechanical ventilation or the length of hospital stay. Limitations of the study include the lack of information on Ta1 dose and duration of treatment in two of the studies, and the retrospective design of most of the studies. Because many of the studies were conducted early in the pandemic, it is unclear if the results would be reproducible in patients hospitalized with the current circulating viral strain and with the use of current medications that were not available at the time that many of these studies were conducted.

Wu et al. 2023: In this small retrospective cohort study of 219 hospitalized adults on hemodialysis infected with the Omicron strain of SARS-CoV-2, the authors divided the subjects into two groups (severely ill, n=78, or not, n=141) and used a multiple regression analysis to identify risk factors for severe illness. The severely ill subjects were subdivided into those who were discharged (n=53) or those who died (n=25), and the treatment drugs were analyzed to identify risk factors or protective factors for death. The authors report that Ta1 increased the probability of discharge. The types of treatment used included Ta1, interferon, remdesivir, globulin, hormones, Tanreqing, antibiotics, high flow oxygen, and continuous renal replacement therapy (CRRT). The authors do not report the dose, ROA, or frequency of Ta1 exposure. The authors do not define clearly how the severity of disease was determined. They report that the

severe group required intensive care or were severely ill within 49 hours of hospital admission, but they do not report whether these subjects needed mechanical ventilation, or which subjects received which treatments.

For completeness, we included a review article by Dinetz and Lee (2024), which claims that there is evidence of Ta1's effectiveness in the treatment of several diseases, including COVID-19. This review included the following articles:

1. Shang et al. 2023 was a meta-analysis that is discussed above.
2. Tuthill et al. 2023 was a prospective trial in which 194 adults with end stage renal disease were given either standard therapies or standard therapies and Ta1 (also referred to in the article as thymalfasin and Zadaxin) 1.6 mg SC twice a week for 8 weeks to see if receiving Ta1 prevented COVID-19 infection. The study was conducted from January 2021 to July 1, 2022. The published article stated that evaluation of efficacy endpoints had not yet been completed.
3. Wang et al. 2021b was a retrospective cohort study conducted from January to March 2020 in hospitalized adults with COVID-19. Subjects received either standard of care or standard of care and Ta1 given via SC ROA at a dose of 1.6 mg twice a week until improvement of disease (duration in number of treatment days was not provided). The primary endpoint was change in CD4+ and CD8+ T cell counts following admission in the control vs. Ta1 groups. The authors report that use of Ta1 had no effect on promoting the recovery of CD4+ and CD8+ T cell counts. They also report no differences in the clearance time of virus and duration of hospitalization between the control and Ta1 groups. Limitations of this study include its retrospective design, the date of data collection being early in the pandemic and not reflecting the current circulating strain, and the endpoints evaluated (cell counts) being of unclear clinical significance.
4. Li et al. 2021 was included in the meta-analysis by Soeroto et al. 2023 described above. This study was a retrospective cohort study in which 78 hospitalized adults with COVID-19 received either standard of care or standard of care and Ta1 1.6 mg via the SC ROA for 15 days. Data was collected from January through April 2020. The authors evaluated levels of lymphocyte subsets and cytokines before and after Ta1 to see if levels were different in men and women. Limitations of this study include the small sample size, the date of data collection being early in the pandemic, and the endpoints evaluated being of unclear clinical significance.

b. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

Some people infected with SARS-CoV-2 have mild COVID-19 illness, and others have no symptoms. In some cases, however, COVID-19 can lead to respiratory failure, lasting lung and heart muscle damage, nervous system problems, kidney failure or death.[154] Therefore, COVID-19 is a potentially serious or life-threatening disease.

[154] https://www.hopkinsmedicine.org/health/conditions-and-diseases/coronavirus. Accessed June 6, 2024.

c. Therapies that have been used for the condition(s) under consideration

There are FDA-approved drug products that treat the same medical condition as FDA has evaluated for the proposed compounded drug product containing Ta1-related BDSs. The following list includes currently available FDA-approved drug products indicated for COVID-19:

- Remdesivir, IV (Veklury), a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleotide analog RNA polymerase inhibitor indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (birth to less than 18 years of age weighing at least 1.5 kg) who are hospitalized, or not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

- Baricitinib, oral (Olumiant), a Janus kinase (JAK) inhibitor indicated for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

- Tocilizumab, IV(Actemra), an interleukin-6 (IL-6) receptor antagonist indicated for the treatment of hospitalized adult patients with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

FDA is aware that certain FDA-approved drug products have been used off-label for the same medical condition as FDA has evaluated for the proposed compounded drug products containing Ta1-related BDSs. These include:

- Dexamethasone Sodium Phosphate Injection, a corticosteroid, is an FDA-approved drug that has been used off-label for the treatment of hospitalized patients with COVID-19 who require supplemental oxygen based on NIH treatment guidelines.[155]

d. Conclusion

There is insufficient information concerning effectiveness to support the use of SC Ta1 for the treatment of COVID-19. Three of the four meta-analyses reviewed concluded that there was no decrease in mortality in subjects treated with Ta1. Studies of the effectiveness of Ta1 for COVID-19 were limited by small sample sizes and deficient study designs (e.g., retrospective, lack of blinding), as well as the use of concomitant medications. In addition, most of the studies were conducted early in the pandemic, and it is unclear if the outcomes would be reproducible

[155] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://wayback.archive-it.org/4887/20240626155414/https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf and https://wayback.archive-it.org/4887/20240626155208/https://www.covid19treatmentguidelines.nih.gov/ Accessed October 8, 2024. Additional Treatment Guidelines can be found at the Infectious Diseases Society of America website (IDSA Guidelines on the Treatment and Management of Patients with COVID-19) at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed October 8, 2024.

given the current circulating viral strain and changes in treatments since the studies were completed. There was heterogeneity between studies in the definition of disease severity, and dose and frequency of exposure to Ta1 (in some studies the dose and frequency was not reported), making it difficult to compare the study outcomes. NIH and WHO treatment guidelines do not discuss the use of Ta1 for COVID-19. COVID-19 can be a serious condition and there are FDA-approved therapies with established efficacy for COVID-19.

5. Depressed response to vaccinations; adjuvant to flu vaccine

The nomination proposed Ta1 for use as an "**adjunct** to flu vaccine" in the following condition "requiring immune response modulation: for depressed response to vaccinations." We consider this use, as described, to be an adjuvant, which is a component of an adjuvanted vaccine.

A vaccine "adjuvant" can be used as a component of a vaccine, and the terminology informs the specific context of use. A vaccine adjuvant is a substance added to some vaccines to enhance the immune response of vaccinated individuals to the vaccine antigen(s). Vaccine adjuvants may be used in conjunction with a vaccine antigen to enhance (e.g. increase, accelerate, prolong and/or possibly target) or modulate to a different type (e.g., switch a Th1 immune response to a Th2 response, or a humoral response to a cytotoxic T-cell response) the specific immune response to the vaccine antigen in order to enhance the clinical effectiveness of the vaccine.[156]

When evaluating a vaccine for safety and effectiveness, FDA considers adjuvants as a component of a vaccine, and adjuvants are not approved separately.[157] Adjuvants are not licensed for use alone. Only, a specific adjuvant/antigen combination is licensed. It should be noted that when an adjuvant is added to a previously unadjuvanted vaccine, the adjuvanted formulation of the vaccine would be considered a new investigational product, subject to requirements for unapproved vaccines (e.g., submission of a new investigational drug application (IND) if appropriate). FDA's constituent materials regulation (21 CFR 610.15(a)) states that "[a]n adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product." Several adjuvanted vaccines are licensed in the United States.[158] The advantages of adjuvants, when supported by appropriate data, can include the enhancement of the immunogenicity of antigens, modification of the nature of the immune response, the reduction of the amount of antigen needed for a successful immunization, reduction of the frequency of booster immunizations needed, and an improved immune response in elderly and immunocompromised vaccinees (European Medicines Agency Evaluation of Medicines for Human Use, 2005).

Because no drug product is FDA-approved for use as an "adjunct to flu vaccine" or with other vaccines in the manner proposed in the nomination, we assessed the article, Tuthill and King (2013), included in the nomination to inform our understanding of the proposed use of a vaccine adjuvant. The article discussed "Ta1 use in vaccine enhancement" because of its "immune

[156] Available at https://www.who.int/publications/m/item/nonclinical-evaluation-of-vaccine-adjuvants-and-adjuvanted-vaccines-annex-2-trs-no-987. Accessed June 28, 2024.
[157] Available at https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/common-ingredients-fda-approved-vaccines. Accessed June 28, 2024.
[158] Available at https://www.cdc.gov/vaccine-safety/about/adjuvants.html. Accessed June 28, 2024.

enhancing effect" when it was administered separately to elderly subjects who had received influenza vaccination to augment vaccine efficacy. Ta1 was used similarly in subjects who were "immunocompromised by chronic renal failure and undergoing hemodialysis." However, in the studies referenced by the authors, they discuss Ta1 when used as "**adjuvant** for influenza or hepatitis B vaccines" after receiving either of these vaccines.

In addition to assessing the articles included in the nomination to inform our understanding of the proposed use, we considered five clinical studies that we identified in which Ta1 was administered simultaneously or immediately after an influenza vaccine (See Section II.D.5.a). These studies evaluated immune responses to vaccination in difficult-to-treat populations, including individuals immune suppressed due to age or subjects with end-stage-renal disease (ESRD) on hemodialysis.

We limited our evaluation to Ta1 used as an "adjuvant" with influenza vaccine in elderly and ESRD subjects based on the context of use proposed in the nomination and described in the publications that were considered.

Considerations for Assessing Effectiveness

FDA relies on the evaluation of functional antibodies, such as hemagglutination inhibiting (HI) or neutralizing (NT) antibodies to measure immune response for influenza vaccines. The use of Enzyme-Linked Immunosorbent Assay (ELISA) to measure antibodies to a strain-specific antigen may not meet the standards used by FDA and other global regulators to evaluate immune responses to influenza vaccines.

For inactivated influenza vaccines containing viral hemagglutinin, an HI titer of 1:40 for each of the influenza viral strain used in the vaccine may be a reasonable serologic measure of protection against clinical symptoms of influenza. Increases in titer do not necessarily translate to enhanced protection against influenza disease.

The antibody levels that are critical for protection against influenza will likely vary among populations (e.g., elderly and pediatric), influenza strains, and vaccine types (e.g., new manufacturing platforms or novel constructs).

a. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

We identified five clinical studies of Ta1 as an adjuvant to influenza vaccine in elderly and ESRD subjects (Gravenstein et al. 1986, Gravenstein et al. 1989, McConnell et al 1989, Shen et al. 1990, Carraro et al. 2012). Of these, two clinical studies (Gravenstein et al. 1986, McConnell et al. 1989) were retrieved as abstracts and we were unable to identify full-text articles. These two studies were cited in other review articles (Ershler et al. 2007, Guay 2010, Panatto et al. 2011 and Tuthill et al. 2012).

Gravenstein et al. (1986): The authors conducted a pilot trial of the anti-influenza antibody response of Ta1 on influenza vaccination in nine elderly subjects who had been nonresponsive to

seasonal trivalent influenza vaccination in the previous year. The subjects received Ta1 0.9 mg/m^2 SC injection twice weekly for 5 weeks following a single injection of seasonal influenza vaccine. Six controls received only influenza vaccine. Response was defined as an increase in serum anti-influenza antibody titers measured by ELISA or by a fourfold change in hemagglutination titer.

The authors reported that six of the nine subjects (67%) showed "high levels" of anti-influenza antibodies, compared to a historical rate of 10% after revaccination in elderly subjects. The term "high levels" used by the author is a qualifying statement that was not supported by data; indeed, no data were included in this abstract. As noted, this was a pilot trial and the information in the abstract was inadequate to interpret effectiveness.

Gravenstein et al. (1989): Based on the results of the (above) pilot trial the authors conducted a R, DB, PC study of Ta1 on the influenza antibody response in 90 elderly male veterans (age >65 years). Subjects were randomized to receive SC injections of Ta1 0.9 mg/m^2 (n=46) or placebo (n=44) twice weekly for 4 weeks, with the first dose given immediately after the 1986 influenza vaccine (Fluzone) containing 15 µg each of the A/Chile/1/83 (H1N1), A/Mississippi/1/85 (H3N2) and B/Ann Arbor/1/86 hemagglutinins. The first coat antigen was either the purified hemagglutinin subunit (the hemagglutinin of one of the three strains) or a mixture of the three (trivalent antigen). Anti-influenza antibodies were measured by ELISA adapted from Murphy et al. (1981). Eighty-five subjects were analyzed because several did not meet the age requirement, dropped out or died. The subjects were examined before vaccination and every 14 days for 6 weeks, and at 6 months for AEs.

The authors reported that the antibody response rate (four-fold increase in ELISA antibody titer at 3-6 weeks after vaccination), was similar in both treatment groups until 6 weeks post vaccination. Of the 45 subjects who received Ta1, 31 (69%) achieved a fourfold increase in antibody titer compared to 21 of the 40 (52%) who received in the placebo. In a subgroup analysis by mean age (older group 77 years and older, and younger group 65-76 years), antibody levels in the younger group were comparable in both treatment groups at 6 weeks post vaccination. In the older group, the antibody level was higher in the Ta1 group than in the placebo group. The absolute amount of antibody produced was sustained in the Ta1 treatment group but decreased in the placebo group. The antibody levels in the Ta1 group were similar regardless of age whereas those in the placebo group declined with advancing age.

Because of the small size of study subgroups and use of ELISA as an outcome measure, the utility of the results of this 35-year-old study are questionable and should be interpreted with caution. Additionally, the study was conducted before the licensure of influenza vaccines recommended for use in the elderly (i.e., Fluad, Fluzone High-Dose and Flublok), which are considered the standard of care in this population. Whether Ta1 provides a clinical benefit in current settings is unknown because the elderly male subjects included in these studies did not receive the contemporary U.S. standard of care.

McConnell et al (1989): The R, DB trial evaluated the response to influenza vaccination with or without Ta1 in 337 elderly subjects from the United States Soldiers' and Airmen's Home in Washington, DC. The age range was 65 to 101 years (median 73 years). All the subjects received

trivalent seasonal influenza vaccine (B/Ann Arbor, A/H3N2 Leningrad, A/H1N1 Taiwan). The subjects were randomized to one of three treatment groups. Group 1 received twice weekly Ta1 (0.9 mg/m^2) for a total of eight doses (4 weeks); group 2 received the same dose of Ta1 but only for four doses (2 weeks) followed by four doses of placebo for the next 2 weeks; group 3 received eight doses (4 weeks) of placebo. The number of subjects in each group was not stated. Ta1 injections were initiated immediately after trivalent seasonal influenza vaccination. Serum IgG was measured by ELISA at 4, 6-, 8-, 14, - and 18-weeks post-vaccination. No description of the assay methodology or antigens used was provided in this abstract.

The study authors reported that subjects in group 1 had a higher H1N1 Taiwan antibody concentration compared with the other two groups. Subjects over 80 years of age had higher antibody levels for B/Ann Arbor and A/H3N2 Leningrad. Without information regarding the assay, and methodology of the assay, it is impossible to ascertain the validity of these data. Moreover, ELISA does not measure a functional antibody response and is not used by FDA to assess the immune response to influenza in clinical studies. The timepoints of the observations are not mentioned, and baseline values by group were not shown. According to the article, "the attack rate was reduced (6/110 vs 21/110)", however, which of the three groups to which these subjects belonged was not stated. The study was presented as abstract with few details. In the absence of critical information, the results cannot be accurately evaluated.

Shen et al. (1990): This R, DB, PC study evaluated the effect of Ta1 on antibody production after influenza vaccination and the correlation of age and duration of ESRD prior to vaccination on anti-influenza antibody response in 97 subjects on chronic hemodialysis. Group A (n=48) received influenza vaccine containing A/Taiwan/1/86 (H1N1) antigen and SC injection of Ta1 (0.45 ml/m^2 = 0.9 mg/m^2) twice weekly for 4 weeks with the first dose given simultaneously with the vaccine. Group B (n=49) received an influenza vaccine and SC injection of placebo (thymosin diluent). Both Ta1 and placebo were manufactured by Hoffman-LaRoche, Inc. Sera were collected before vaccination, and at 4 and 8 weeks thereafter. Anti-influenza antibody responses were evaluated by ELISA using an unknown antigen. A positive response to vaccination was defined as an increase in the specific anti-influenza antibody level to fourfold that pre-vaccination at 4 weeks or later post-vaccination. The baseline titers and seropositivity rate were not provided.

This study reported that at 4 weeks postvaccination, 71% (34/48) of the subjects in group A responded to influenza vaccination compared to 43% (21/49) of those in group B. At 8 weeks postvaccination, the response rates were 65% (31/48) in group A and 24% (12/49) in group B. Additionally, 17 subjects in group A and 2 subjects in group B were reported to have an increase in ELISA antibody response more than eightfold greater than that pre-vaccination level at 4 and 8 weeks postvaccination. There were no differences in duration of ESRD at enrollment between responders and non-responders in either group A or B, at 4 or 8 weeks postvaccination. The age range was 22-82 years in group A and 22-70 years in group B. The mean ages of the two groups were comparable (50.5±14.8 and 49.3±13.5 SD, groups in A and B, respectively). In both groups, the mean age of the responders at 4 weeks post-vaccination was lower than that of non-responders (47.9 ± 14.3 vs 53.9 ± 10.8). The response decreased with increasing age in group B but not group A. Due to the small sample sizes and lack of critical information on baseline titers

and meaningful antibody measurements, this study cannot be accurately evaluated for effectiveness.

Carraro et al. (2012): This explorative, OL, R, parallel three arm trial evaluated the effects of two doses of Ta1 (Zadaxin)[159] on the immunogenicity of an egg-derived MF59-adjuvated monovalent A/H1N1 influenza vaccine (Focetria) in 99 subjects with ESRD on dialysis. Of 99 subjects, 5 were excluded due to a lack of observations after the first vaccination. The subjects were randomly assigned to three treatment groups. Treatment group 1 received influenza IM vaccine alone (n= 34), and treatment groups 2 (n=28) and 3 (n= 32) received influenza vaccine plus SC Ta1 (3.2 mg) and influenza vaccine plus SC Ta1 (6.4 mg), respectively. All the subjects received one dose of influenza vaccine on Day 0; those in treatment groups 2 and 3 received Ta1 7 days before and on the day of vaccination (Day 0, – baseline).

Strain-specific antibodies were measured by HI, microneutralization and single radial hemolysis, at 0, 21, 42, 84 and 168 days. Subjects who did not reach a titer of 1:40 received a second dose of a vaccine 18-28 days after the first. The co-primary immunogenicity endpoints were the proportion of subjects with HI antibody titers of 1:40 or more, the proportion of subjects with seroconversion or a significant increase in antibody titer, and the factor increase in geometric mean titer (GMT) in the per-protocol (PP)[160] (n=82) and intention-to-treat (ITT)[161] populations (n=94).

The postvaccination immune response results in the ITT and PP populations are shown in Tables 5 and 6. No information or data were provided on the participants who received a second dose of influenza vaccine.

[159] Ta1 (Zadaxin) is authorized in Italy as a 1.6 mg powder (1.6 mg/mL when reconstituted) for injection for SC or IM injection as "an adjuvant to influenza vaccination in immunocompromised individuals." (See https://www.aifa.gov.it/en/autorizzazione-dei-farmaci. Accessed June 25, 2024.). Zadaxin was provided by Sigma-tau S.p.A. Focetria was provided by Novartis Vaccines and Diagnostics. Focetria is not a US licensed vaccine.
[160] Per-Protocol (PP) are subset of the Intention-To-Treat (ITT) population completing the study treatment, who underwent at least the Day 42 evaluation, and who fulfilled the inclusion criteria of the study protocol and safety population (defined as the subjects who received at least one dose of the trial medications) (Carraro et al. 2012).
[161] Intention-To-Treat (ITT) is defined as subjects who received at least one dose of the trial product and had at least one post-baseline evaluation (Carraro et al. 2012).

Table 5. Evaluation of the Immunoresponse after Vaccine Administration and at Various Time Points During Follow-up, Measured by Hemagglutination–Inhibition (HI) Assay – ITT Population (Carraro et al. 2012).

Evaluation of the immunoresponse after vaccine administration and at various time-points during follow-up, measured by hemagglutination–inhibition (HI) assay – ITT population.

Immunogenicity end point	Vaccine only			Vaccine + 3.2 mg Thymosin α1			Vaccine + 6.4 mg Thymosin α1		
	<61 years	≥61 years	All ages	<61 years	≥61 years	All ages	<61 years	≥61 years	All ages
Baseline									
No.	8	26	34	7	21	28	8	24	32
GMT value	16.1	18.3	17.8	9.5	11.5	11.0	9.8	10.8	10.6
Day 21 (after 1st dose)									
No.	8	26	34	7	21	28	8	24	32
Seroconverted or sign. increasing, no. (%)	4 (50.0)	14 (53.9)	18 (52.9)	7 (100)	18 (85.7)	25 (89.3)	8 (100)	20 (83.3)	28 (87.5)
Seroprotected, no. (%)	5 (62.5)	21 (80.8)	26 (76.5)	7 (100)	19 (90.5)	26 (92.9)	8 (100)	22 (91.7)	30 (93.8)
GMT value	74.9	66.0	68.0	195.0	111.4	128.1	348.5	139.6	175.5
GMR (Day 21/Day 0)	4.7	3.6	3.8	20.5	9.7	11.7	35.6	12.9	16.6
Day 42									
No.	8	26	34	7	21	28	8	24	32
Seroconverted or sign. increasing, no. (%)	6 (75.0)	18 (69.2)	24 (70.6)	7 (100)	19 (90.5)	26 (92.9)	8 (100)	22 (91.7)	30 (93.8)
Seroprotected, no. (%)	7 (87.5)	25 (96.2)	32 (94.1)	7 (100)	21 (100)	28 (100)	8 (100)	24 (100)	32 (100)
GMT value	146.8	128.5	132.6	176.9	127.1	138.1	236.0	142.8	161.9
GMR (Day 42/Day 0)	9.1	7.0	7.5	18.6	11.0	12.6	24.1	13.2	15.3
Day 84									
No.	8	26	34	7	21	28	8	24	32
Seroconverted or sign. increasing, no. (%)	6 (75.0)	16 (61.5)	22 (64.7)	5 (71.4)	10 (47.6)	15 (53.6)	7 (87.5)	14 (58.3)	21 (65.6)
Seroprotected, no. (%)	7 (87.5)	22 (84.6)	29 (85.3)	5 (71.4)	13 (61.9)	18 (64.3)	7 (87.5)	17 (70.8)	24 (75.0)
GMT value	140.3	84.5	95.2	59.5	36.6	41.3	101.7	50.0	59.8
GMR (Day 84/Day 0)	8.7	4.6	5.4	6.3	3.2	3.8	10.4	4.6	5.7
Day 168									
No.	8	26	34	7	21	28	8	24	32
Seroconverted or sign. increasing, no. (%)	3 (37.5)	6 (23.1)	9 (26.5)	2 (28.6)	5 (23.8)	7 (25.0)	5 (62.5)	9 (37.5)	14 (43.8)
Seroprotected, no. (%)	4 (50.0)	14 (53.9)	18 (52.9)	2 (28.6)	9 (42.9)	11 (39.3)	5 (62.5)	10 (41.7)	15 (46.9)
GMT value	47.5	41.1	42.6	31.3	22.1	24.1	61.8	32.2	37.9
GMR (Day 168/Day 0)	3.0	2.2	2.4	3.3	1.9	2.2	6.3	3.0	3.6

Note: The immunogenicity end-points were: the proportion of subjects who had an antibody titer of 1:40 or more, the proportion of subjects who had either seroconversion (a pre-vaccination titer less than 1:10 with a post-vaccination antibody titer of 1:40 or more measured by HI assay) or a 4-fold increase in antibody titer, and a factor increase in the geometric mean titer.

Table 6. Evaluation of the Immunoresponse after Vaccine Administration and at Various Time Points During Follow-up, Measured by Hemagglutination–Inhibition (HI) Assay – PP Population (Carraro et al. 2012).

Evaluation of the immunoresponse after vaccine administration and at various time-points during follow-up, measured by hemagglutination–inhibition (HI) assay – PP population.

Immunogenicity end point	Vaccine only			Vaccine + 3.2 mg Thymosin α1			Vaccine + 6.4 mg Thymosin α1		
	<61 years	≥61 years	All ages	<61 years	≥61 years	All ages	<61 years	≥61 years	All ages
Baseline									
No.	7	20	27	6	21	27	7	21	28
GMT value	17.2	19.2	18.6	10.6	11.5	11.3	10.8	10.6	10.6
Day 21 (after 1st dose)									
No.	7	20	27	6	21	27	7	21	28
Seroconverted or sign. increasing, no. (%)	4 (57.1)	11 (55.0)	15 (55.6)	6 (100)	18 (85.7)	24 (88.9)	7 (100)	18 (85.7)	25 (89.3)
Seroprotected, no. (%)	5 (71.4)	16 (80.0)	21 (77.8)	6 (100)	19 (90.5)	25 (92.6)	7 (100)	20 (95.2)	27 (96.4)
GMT value	99.9	70.3	77.0	253.8	111.4	133.7	319.6	141.4	173.4
GMR (Day 21/Day 0)	5.8	3.7	4.1	24.0	9.7	11.8	29.7	13.3	16.3
Day 42									
No.	7	20	27	6	21	27	7	21	28
Seroconverted or sign. increasing, no. (%)	6 (85.7)	15 (75.0)	21 (77.8)	6 (100)	19 (90.5)	25 (92.6)	7 (100)	19 (90.5)	26 (92.9)
Seroprotected, no. (%)	7 (100)	20 (100)	27 (100)	6 (100)	21 (100)	27 (100)	7 (100)	21 (100)	28 (100)
GMT value	215.5	156.0	169.6	190.6	127.1	139.1	237.5	136.0	156.3
GMR (Day 42/Day 0)	12.5	8.1	9.1	18.0	11.0	12.3	22.1	12.8	14.7
Day 84									
No.	7	20	27	6	21	27	7	21	28
Seroconverted or sign. increasing, no. (%)	6 (85.7)	12 (60.0)	18 (66.7)	4 (66.7)	10 (47.6)	14 (51.9)	6 (85.7)	12 (57.1)	18 (64.3)
Seroprotected, no. (%)	7 (100)	17 (85.0)	24 (88.9)	4 (66.7)	13 (61.9)	17 (63.0)	6 (85.7)	14 (66.7)	20 (71.4)
GMT value	204.7	95.3	116.2	63.5	36.6	41.3	95.3	46.0	55.2
GMR (Day 84/Day 0)	11.9	5.0	6.2	6.0	3.2	3.7	8.9	4.3	5.2
Day 168									
No.	7	20	27	6	21	27	7	21	28
Seroconverted or sign. increasing, no. (%)	3 (42.9)	4 (20.0)	7 (25.9)	2 (33.3)	5 (23.8)	7 (25.9)	4 (57.1)	8 (38.1)	12 (42.9)
Seroprotected, no. (%)	4 (57.1)	10 (50.0)	14 (51.9)	2 (33.3)	9 (42.9)	11 (40.7)	4 (57.1)	8 (38.1)	12 (42.9)
GMT value	59.4	40.8	45.0	35.7	22.1	24.6	53.9	32.8	37.2
GMR (Day 168/Day 0)	3.4	2.1	2.4	3.4	1.9	2.2	5.0	3.1	3.5

Note: The immunogenicity end-points were: the proportion of subjects who had an antibody titer of 1:40 or more, the proportion of subjects who had either seroconversion (a pre-vaccination titer less than 1:10 with a post-vaccination antibody titer of 1:40 or more measured by HI assay) or a 4-fold increase in antibody titer, and a factor increase in the geometric mean titer.

Study findings showed that the proportion of subjects with a baseline antibody titer ≥ 1:40 was higher in the vaccine-only group than in the vaccine plus Ta1 groups. The GMT, geometric mean titer ratio (GMR) of HI, and the proportion of subjects who seroconverted or achieved an HI titer ≥1:40 were higher in the vaccine plus Ta1 groups than the vaccine-only groups in the ITT and PP populations on day 21. The authors stated that the results of HI assay for seroconversion, "seroprotection" (i.e., titer ≥1:40) and the GMR on day 21 were in agreement with the Committee for Medicinal Products for Human Use (CHMP) criteria, even though the number of subjects was small, and were in agreement with Evaluation of Medicinal Products (EMA) guidelines for registration of a seasonal influenza vaccine. Importantly, on days 42, 84 and 168, the percentages of subjects who had seroconverted and were seroprotected, GMT, and GMR were higher in the vaccine-only group than in the vaccine plus Ta1 groups. The GMT values for administration of vaccine alone in subjects > 61 years of age were 128, 84 and 41 units, compared to 127, 36 and 22 units with the addition of 3.2 mg of Ta1. The authors reported that "On days 84 and 168, both the percentages of subjects who had seroconverted and seroprotected, GMT and GMR were higher in the vaccine-only group than in the vaccine plus Ta1 groups."

Slightly different antibody responses were determined by microneutralization (MN) assay. The GMT values by MN assay were highest in the vaccine + Ta1 6.4 mg group in the PP and ITT populations at each time-point of follow-up. However, the GMT values were higher in the vaccine-only group than in the vaccine + Ta1 3.2 mg group in the PP and ITT populations.

The GMT response decreased significantly after day 21 when Ta1 1.6 mg/mL was used with the Focetria influenza vaccine. However, we are unsure whether the addition of Ta1 at the strength proposed in the nomination (3 mg/mL) would further reduce the immune response to the vaccine. The authors concluded that administration of influenza vaccine in conjunction with Ta1 may strengthen the immune response and improve vaccine safety in both immunocompetent and immunocompromised subjects. However, based on the HI results, the Ta1 titers indicated a numerical increase in antibody titer only on day 21, suggesting that Ta1 does not contribute to sustained antibody responses or provide long-term benefits. Based on the study results, it may be possible that Ta1 interfered with the sustained immune response of the participants. As such, these data are not supportive of use of Ta1 as an effective, or even useful, vaccine adjuvant.

Summary of Efficacy Studies

The five published studies evaluated doses of 0.9 mg/m^2 to 6.4 mg/m^2 administered in a different number of doses and timepoints in relation to vaccination, which in some studies consisted of monovalent or trivalent influenza vaccines (Table 7).

Table 7. Summary of Study Designs of Clinical Studies Evaluating Ta1 as an Adjuvant to Influenza Vaccine.

Study Population (Publication)	N	Described Ta-1 Dose/regimen	Monovalent or Trivalent Influenza Vaccine
Elderly subjects (pilot study) (Gravenstein 1986)	9	0.9mg/m^2 twice weekly for 5 weeks after vaccination	Influenza seasonal trivalent
Elderly male veterans (Gravenstein 1989)	90	0.9mg/m^2 twice weekly for 4 weeks after vaccination	Influenza seasonal trivalent
Elderly male veterans (McConnell 1989)	330	0.9mg/m^2 twice weekly for 2 or 4 weeks after vaccination	Influenza seasonal trivalent
Patients on hemodialysis (Shen 1990)	97	0.9mg/m^2 twice weekly for 4 weeks after vaccination	Influenza H1N1 monovalent
Chronic patients 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

Carraro et al. (2012) did not use an adequate number of subjects to assess meaningful differences in outcomes between groups. Furthermore, the GMT response decreased significantly for Ta1 1.6 mg/mL with the Focetria influenza vaccine. The limited data did not suggest an increase in antibody responses beyond 21 days, suggesting that Ta1 does not contribute to sustained antibody responses or provide long-term benefits and that Ta1 interfered with the sustained immune response in all populations in the study.

ELISA was used in some of the studies. This method measures only antibody binding and does not assess functional activity, such as HI or NA. A validated serum HI assay with standardized reference standards is used to evaluate the immune responses to influenza for the purpose of making regulatory decisions.

All the cited studies were exploratory and lacked formal hypothesis testing and prespecified immunogenicity or efficacy endpoints. Gravenstein et al. (1986) and McConnell et al. (1989) lacked sufficient information to interpret effectiveness, being available only as abstracts. The heterogeneity in the data make it difficult to infer vaccine effectiveness from antibody responses, or to establish an optimal dose and regimen of Ta1 to augment influenza vaccine antibody responses for a proposed use.

Regarding adjuvants in immunosuppressed individuals, such as the elderly, the FDA approved Fluzone High Dose in 2009 and Fluad (under Accelerated Approval) in 2015 specifically for adults 65 years of age and older. Fluzone High Dose contains increased amounts of vaccine antigens and Fluad contains an adjuvant to boost the immune response in the elderly. The use of Ta1 with seasonal influenza vaccines has not been evaluated with adequate controls in the

elderly, or in any population. A population with an unmet medical need, such as elderly individuals or patients with chronic renal disease on hemodialysis, would need to be appropriately identified who may potentially benefit from Ta1 as an adjuvant to seasonal influenza vaccines. Non-responders among the elderly should be defined as those who did not achieve adequate immune responses to influenza vaccines specifically designed to be used in the elderly, which have an increased amount of antigen or contain an adjuvant, both of which are considered the standard of care for this immunosuppressed population and are recommended by the Centers for Disease Control (CDC).[162] Adding an immunomodulatory product such as Ta1 to any vaccine could pose additional, significant safety concerns that warrant further evaluation in an adequate and well controlled clinical study. Furthermore, none of the studies used any of the licensed influenza products (Fluzone, Fluad or Flublok).

Therefore, definitive conclusions on the effectiveness of influenza vaccines, with or without adjuvants, cannot be based solely on the limited immunogenicity evaluation used by the studies considered in this evaluation. To be approved, influenza vaccines that contain an adjuvant component and that have not been previously reviewed by FDA need to be appropriately evaluated. Based on these reports, it is difficult to assess the effectiveness of the immune "enhancement" properties of Ta1 when used with influenza vaccines.

b. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

Influenza occurs seasonally, causing serious disease that results in widespread morbidity and mortality worldwide with a substantial health burden (Smetana et al. 2018). Notably, the clinical burden of influenza disproportionately impacts the most vulnerable individuals including older adults and those of any age with multiple morbidities or immunodeficiency (Incalzi et al. 2024).

c. Therapies that have been used for the condition(s) under consideration

There are FDA-approved vaccines that include adjuvant components that address the same medical conditions as proposed for the Ta1 compounded drug product.[163]

d. Conclusion

There is insufficient evidence to reach a conclusion on the use of Ta1 as an effective vaccine adjuvant or "enhancement." Although the studies evaluated noted that administration of Ta1 in conjunction with influenza vaccine increased and sustained the antibody response in the elderly and subjects with ESRD with or without hemodialysis, conclusions cannot be reached solely on the immunogenicity outcomes evaluated in the studies considered in this evaluation. The magnitude and type of change in the immune responses to vaccination with the addition of Ta1 (increase, no change, decrease) are highly variable across studies. Because of the uncertainty and

[162] Available at https://www.cdc.gov/flu/hcp/acip/. Accessed June 28, 2024.
[163] Available at https://www.cdc.gov/vaccine-safety/about/adjuvants.html. Accessed June 28, 2024.

lack of correlation with clinical outcomes, it is difficult to assess Ta1's effectiveness for the prevention or amelioration of clinical influenza disease or reduction in morbidity and mortality.

Interpretation of effectiveness in these studies is limited. The studies were exploratory, with different designs and treatment regimens, evaluated different doses and regimens, used monovalent or trivalent influenza vaccines, used vaccines in a manner not considered for products licensed for use in the United States, involved one or more immunological endpoints and descriptive statistics, and had treatment arms with small numbers of subjects. Together, these study limitations make it difficult to reach a conclusion on the effectiveness of Ta1 for this use.

The small studies evaluated Ta1 from more than one manufacturer and were used either before or after vaccination with monovalent or trivalent influenza vaccines (adjuvanted or not) at varying doses. None of the studies evaluated Ta1 with a high-dose or adjuvanted influenza vaccine marketed in the United States, the current standard of care for the elderly population in the United States and the most appropriate comparator for the intended use of Ta1 to enhance seasonal influenza vaccination in the elderly. Because the populations of these studies did not receive the contemporary U.S. standard of care, whether Ta1 provides a clinical benefit in current settings is unclear.

We also note that the use of a 3 mg/mL concentration of Ta1 is proposed in the nomination, but the nomination includes no information on the appropriate Ta1 dose for this use (as opposed to concentration of Ta1 used for administration) or the dose or regimen of influenza vaccination with which the compounded Ta1 drug product should be administered. Based on the limited study data available, this additional information on dosing is critical to our ability to draw any conclusions regarding the efficacy of Ta1 when used with vaccines. Without additional information, it is unclear whether Ta1 would be effective for use proposed in the nomination.

6. Malignant Melanoma

Melanoma arises from a malignant transformation of melanocytes (the cells that synthesize melanin, a photoprotective pigment). Metastatic melanoma is the spread of primary melanoma cells to distant organs such as lymph nodes, lungs, liver, brain, and bones (Sundararajan et al. 2024). Once diagnosed, melanoma is usually categorized by the American Joint Committee on Cancer (AJCC) TNM staging system as local disease (stage I-II), node-positive disease (stage III), or advanced/metastatic disease (stage IV) (Jenkins and Fisher, 2021). The TNM stage and presence/absence of a BRAF V600E/K[164] mutation (for patients with stage III-IV) are the most crucial features used in determining eligibility for FDA-approved immunotherapy or targeted therapy options (Jenkins and Fisher 2021).

The treatment of metastatic melanoma has advanced significantly in the last decade. Before 2011, treatment with chemotherapy had been the standard of care for melanoma patients; the median survival of patients with advanced melanoma was 6–9 months, with only 25% alive at 1 year and <10% at 5 years (Trojaniello et al. 2021). Since 2011, with the approval of novel therapies (immune checkpoint inhibitors and targeted therapy), the 5-year survival rates have

[164] Approximately half of cutaneous melanomas harbor BRAF mutations, with BRAF V600E/K mutations being the most common (90%) abnormality in the BRAF gene (Jenkins et al. 2021).

increased to greater than 50% (Kahlon et al. 2022), leading to a profound paradigm shift in treatment of the disease. There are several FDA-approved products available for the treatment of unresectable or metastatic melanoma (Section II.D.6.c).

In the United States, guidelines for systemic therapy for melanoma are available from the American Society of Clinical Oncology (ASCO) (Seth et al. 2023) and the National Comprehensive Cancer Network (NCCN) (Swetter et al. 2024). The ASCO and NCCN guidelines do not mention Ta1 in their recommendations.

a. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

Ta1 was proposed for the use of malignant melanoma (also known as melanoma). In addition, based on studies of Ta1, FDA considered the use of Ta1 as an adjunct to chemotherapy in the context of the nominated condition of malignant melanoma. The NCI defines **adjunct** therapy as another treatment used together with the primary treatment; its purpose is to assist the primary treatment.[165] Therefore, studies investigating Ta1 as an adjunct would need to demonstrate that the addition of Ta1 provides a clear benefit over the therapeutic backbone to which it has been added. Furthermore, in the case of melanoma, the use of chemotherapy as a standard of care has been decisively eclipsed by immunotherapies and targeted therapies. Therefore, any investigation into the use of Ta1 as an adjunct to chemotherapy would be irrelevant given present-day treatment paradigms.

We identified four published studies using Ta1 in patients with metastatic melanoma, a subtype of melanoma.[166] These studies are summarized in Appendix 1 and are organized chronologically. In these studies, authors reported on overall survival (OS), in addition to multiple other endpoints. In the prospective studies (Lopez et al. 1994; Maio et al. 2010; Rasi et al. 2000), Ta1 was administered as a SC injection with daily doses ranging from 1 to 6.4 mg/day in combination with dacarbazine (DTIC) and IFN-alpha or interleukin-2 (IL-2). We did not identify any studies in which Ta1 was administered as monotherapy in patients with metastatic melanoma.

It is not possible to draw any meaningful conclusions regarding the effectiveness of Ta1 from the Lopez et al. (1994) and Rasi et al. (2000) studies because they were single arm studies in which patients received Ta1 in combination with DTIC and IFN-alpha or IL-2. Thus, it is not possible to determine the contribution of Ta1 or whether its addition to these therapies improved the treatment effect.

Additionally, it is not possible to draw any meaningful conclusions from the Danielli et al. (2018) study because it was retrospective. Although the authors suggested that OS was increased in patients sequentially treated with Ta1 and ipilimumab (vs ipilimumab without previous Ta1 treatment), they note that the retrospective nature of the data and the heterogeneity of patients may have generated bias, requiring the prospective evaluation of Ta1 and ipilimumab

[165] See https://www.cancer.gov/publications/dictionaries/cancer-terms. Accessed May 14, 2024.
[166] We identified one additional review article from Danielli et al. 2012 referencing single institution experience with Ta1 and DTIC in 31 malignant melanoma patients; but we could not find an associated published article.

sequence in a larger number of patients. Data collected retrospectively is confounded by other factors and it is not possible to attribute a difference to the causal relationship of treatment-outcome.

Maio et al (2010) was an exploratory, multicenter, OL, R study in 488 patients with stage IV melanoma with unresectable metastases. The study was designed to assess whether Ta1 could potentiate the efficacy of DTIC (with or without IFN-alpha) in the treatment of metastatic melanoma. Patients were randomized to one of five treatment groups: DTIC+IFN-alpha+Ta1 (1.6 mg) (DIT 1.6 group); DTIC+IFN-alpha+Ta1 (3.2 mg) (DIT 3.2 group); DTIC+IFN-alpha+Ta1 (6.4 mg) (DIT 6.4 group); DTIC+Ta1 (3.2 mg) (DT 3.2 group); and DTIC+IFN-alpha (DI; control group).[167] The primary endpoint was the best overall response rate (ORR; complete responses plus partial responses) at study end (12 months). Per the authors, the overall response rate was expected to be ≤ 5% for standard therapy (P_0) given the patient distribution across AJCC staging criteria and an overall response rate of ≥ 15% would be considered significantly better than standard therapy (P_1). In each treatment arm the null hypothesis ($P_0 \leq 0.05$) was rejected in favor of the alternative hypothesis ($P_1 \geq 0.15$) if nine or more tumor responses were observed at study end. At the end of the study there were 10 and 12 responses observed in the DIT 3.2 mg and DT 3.2 mg groups respectively vs four in the control group (DI), which was sufficient to reject the null hypothesis that $P_0 \leq 0.05$ (expected response rate of standard therapy) in the two arms.

Although the ORR was numerically higher in patients treated with a Ta1 containing regimen vs patients in the control group (DI); this numerical difference was modest, and the ORR did not differ significantly between any of the treatment groups in the ITT population (7.2% DIT 1.6 vs 10.3% DIT 3.2 vs 6.1% DIT 6.4 vs 12.1% DT 3.2 vs 4.1% DI control group). Compared with the control group, there was no statistically significant difference in progression-free survival (PFS) for any of the Ta1-containing groups. There was also no statistically significant

[167] In the original study design patients were randomly assigned in a 1:1:2:2 ratio to one of four treatment arms. A preliminary analysis of the primary endpoint showed a potential dose-response pattern in the DIT 1.6 and DIT 3.2 mg groups and a lower-than-expected overall response rate in the DI (control) group. Consequently, the study sponsor and steering committee requested an extension to the original protocol to incorporate the DIT 6.4 mg group. According to the authors, the extension was requested in consideration of the urgent need for new therapies for melanoma, the favorable safety profile of Ta1 to date, and the exploratory nature of the study.

improvement in OS in any of the treatment arms containing Ta1 (median OS 8.6 to 10.3 months) compared to the control group (median OS 6.6 months) (Figure 9).

Figure 9. Kaplan-Meier Curves for Overall Survival and Progression Free Survival in All Treatment Arms (Maio et al. 2010).

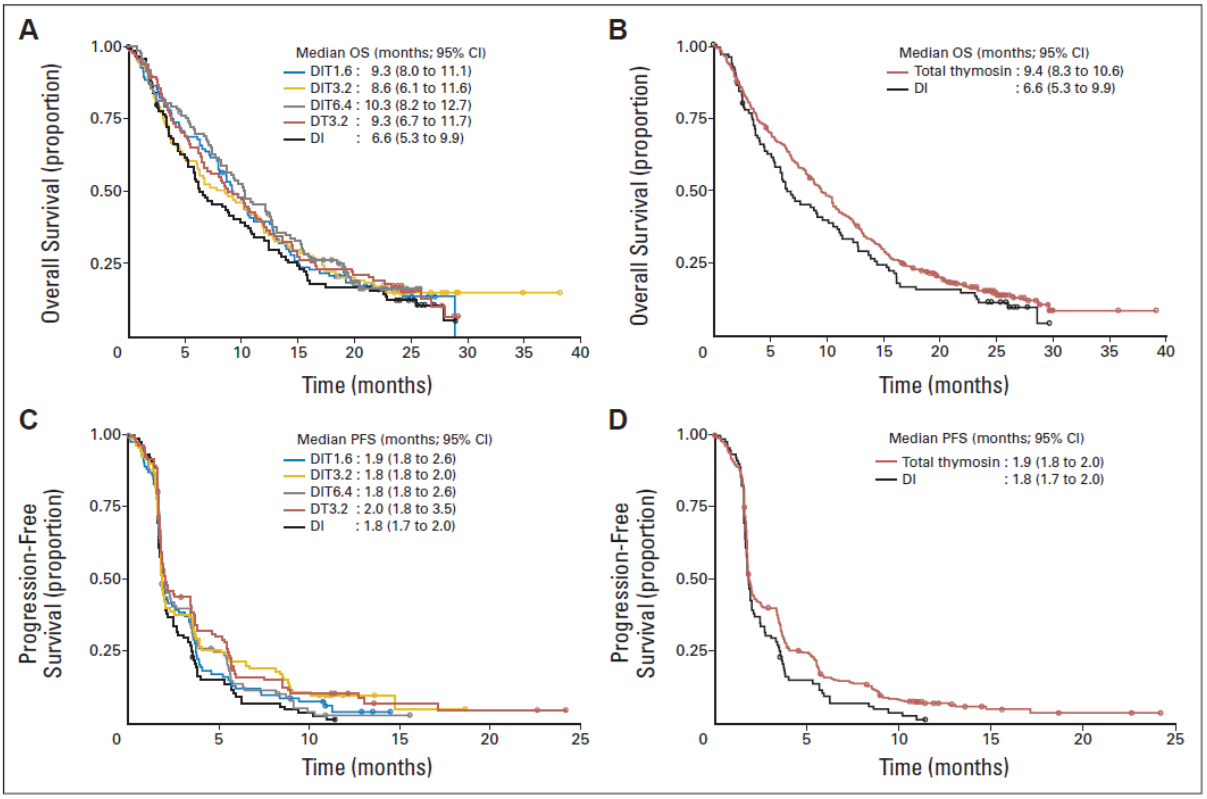

Fig 2. Kaplan-Meier curves for (A, B) overall survival (OS) and (C, D) progression-free survival (PFS) in all treatment arms and in patients treated with any thymosin α 1 (Tα1) –containing regimen. DIT, dacarbazine, interferon alfa, and Tα1; DI, dacarbazine and interferon alfa.

The authors concluded that these results suggest Ta1 has activity in patients with metastatic melanoma and provide a rationale for further clinical evaluation of this agent. The authors do not describe the limitations of the study but do recognize its exploratory nature. In terms of the anti-tumor activity of Ta1 in treating metastatic melanoma, the DIT 3.2 and DT 3.2 arms showed a slight numerical benefit over standard therapy in terms of a predefined ORR based on a comparison with a historical threshold. This numerical increase in response rate was very small and does not represent a clinically meaningful improvement in ORR compared to the control arm. Furthermore, the lower response rate of the DIT 6.4 group compared with the lower dose DIT 3.2 group suggests that these findings may be due to chance. Overall, the study failed to show a significant difference in the ORR with any of the Ta1 containing regimens compared to the control group (DI). In addition, the numerical improvements in PFS and OS were small, and their clinical meaningfulness is difficult to interpret in an exploratory analysis. This study was not adequately designed to demonstrate the contribution of Ta1 to the investigational combination regimens. As such, it is unclear what, if any, additional contribution was provided by Ta1. Of note, the study was conducted when chemotherapy and either interferon or IL-2 was the standard of care. These therapies are rarely, if ever, used in current clinical practice which

greatly limits the generalizability of these results to a US population with unresectable or metastatic melanoma. Additionally, response rates for current standard of care regimens in advanced melanoma, including immunotherapies and targeted therapies (in BRAF mutated disease) are markedly higher (up to 59% using combination immunotherapy regimens (Hodi et al. 2016)) than the historical control data used in this study, which set the expected ORR for standard therapy at ≥ 15%.

We were unable to identify prospective studies comparing Ta1 with current standard of care regimens including checkpoint inhibitor immunotherapy or targeted therapy in patients with metastatic melanoma.

Other Studies

We identified a Cochrane Review that evaluated the effectiveness of purified thymus extracts (thymostimulin or thymosin fraction 5) and synthetic thymic peptides (thymopentin or Ta1) for the management of cancer (Wolf et al. 2011). The authors identified 26 RCTs that met their inclusion criteria; 4 of which used Ta1 (Gish et al. 2009; Maio et al. 2010; Schulof et al. 1985; Cheng et al. 2004). According to the authors, for Ta1, the pooled risk ratio (RR) for OS was 1.21 (95% CI 0.94 to 1.56, P = 0.14), with low heterogeneity; and 3.37 (95% CI 0.66 to 17.30, P = 0.15) for disease-free survival (DFS), with moderate heterogeneity. This was a pooled analysis of studies in multiple types of cancers. Although the authors concluded that there were trends towards reducing the risk of death and disease recurrence with Ta1, statistical significance was not achieved and several of the studies were deemed to be at moderate or high risk of bias.

b. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

Malignant melanoma is serious and life-threatening.

c. Therapies that have been used for the condition(s) under consideration

There are FDA-approved drug products that treat the same medical condition as that proposed for the Ta1 compounded drug product. The NCI maintains a list of currently available FDA-approved drug products indicated for melanoma.[168]

d. Conclusion

The studies investigating the use of Ta1 in melanoma to date are insufficient to demonstrate the effectiveness of Ta1. Although these studies use control data from inferior, outdated regimens (chemotherapy, interferon-alpha), statistically significant, clinically meaningful improvements in Ta1-treated melanoma patients were not demonstrated. A review of the literature identified a single phase 2 randomized clinical study that failed to show a significant difference with any Ta1 containing regimen vs patients in the control group in the ITT population. Based on the study design, it is unclear what, if any, contribution Ta1 provided and if Ta1 is a necessary component

[168] See NIH National Cancer Institute at https://www.cancer.gov/about-cancer/treatment/drugs/melanoma. Accessed June 13, 2024.

of the combination regimens for the observed treatment effect. Of note, this study was conducted when chemotherapy and either interferon or IL-2 were the recommended standard of care. These therapies are rarely, if ever, used in current clinical practice which greatly limits the generalizability of these results to a US population with unresectable or metastatic melanoma. Since publication of this study, several immunotherapies and targeted therapies have been approved; these have demonstrated marked, clinically meaningful and statistically significant improvements in outcomes compared to the control therapies used in the Maio study. 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.

7. Hepatocellular Carcinoma (HCC)

This section focuses on the use of Ta1 in the treatment of HCC. Refer to Sections II.D.1 and II.D.2 for a discussion of the use of Ta1 for the treatment of HBV or HCV infections, which are known risk factors for HCC.

As described below, Ta1 has been studied as an "adjunct" and in the "adjuvant" setting in patients with HCC. The NCI defines **adjunct** therapy as another treatment used together with the primary treatment; its purpose is to assist the primary treatment.[169] Therefore, studies that evaluated Ta1 when used as a chemotherapy adjunct would need to demonstrate whether Ta1, which is not routinely used in the management of HCC, provides a clinical benefit beyond what would be expected for the chemotherapy alone. The NCI defines **adjuvant** chemotherapy as anticancer drugs given after the primary treatment (e.g., surgery) to kill any cancer cells that remain in the body and to lower the risk that the cancer will recur.

HCC is the most common primary liver cancer. The strongest risk factor for HCC is cirrhosis of the liver (from any etiology). The major risk factors for HCC include chronic alcohol consumption, diabetes or obesity-related nonalcoholic steatohepatitis (NASH), and infection by HBV or HCV (Singal et al. 2023). In the US, infection with hepatitis C is the more common cause of HCC, while in Asia and developing countries, hepatitis B is more common.[170]

There are multiple staging systems for HCC, none of which is universally accepted. The most widely used staging system and the one recommended by the AASLD is the Barcelona Liver Clinic Cancer (BCLC) staging system (Singal et al. 2023). The BCLC staging system incorporates performance status, liver burden, and liver function and classifies tumors as very early stage (Stage 0) followed by stages A-D, with Stage D referring to terminal stage (Singal et al. 2023).

Treatment options for patients with HCC include surgical interventions (resection and liver transplantation), locoregional therapies, and systemic therapies, depending on tumor burden, degree of liver dysfunction, and patient performance status (Singal et al. 2023). Curative options such as surgery and some locoregional therapies such as ablation are reserved for early-stage

[169] See https://www.cancer.gov/publications/dictionaries/cancer-terms. Accessed May 14, 2024.
[170] See https://www.cancer.org/cancer/types/liver-cancer/causes-risks-prevention/risk-factors.html. Accessed October 30, 2024.

disease, and other locoregional therapies such as transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and systemic therapy, are used to treat advanced and metastatic disease.

Surgical resection is the curative treatment of choice for patients with localized HCC in the absence of cirrhosis. However, the risk of recurrence following surgical resection is high, approaching 50-70% at 5 years, with the highest risk in the first year after resection (Singal et al. 2023). Factors associated with recurrence include older age, male sex, degree of liver dysfunction, and tumor size, number, and grade/differentiation; microvascular and macrovascular invasion; presence of satellite lesions; and AFP level (Singal et al. 2023).

TACE is the primary treatment option for patients with BCLC Stage B HCC (Singal et al. 2023).[171] Systemic therapy is currently reserved for patients with unresectable HCC who are not suitable for locoregional therapy, including those with advanced-stage HCC (BCLC Stage C), some patients with intermediate-stage HCC (BCLC Stage B), and those who have disease progression despite locoregional therapy (Singal et al. 2023). There are several available FDA-approved products for the treatment of unresectable HCC (Section II.D.5.c).

HCC, unlike many other cancers, lacks an established standard of care for adjuvant treatment. According to a review by Esagian et al. (2021), a variety of strategies using adjuvant therapeutic modalities (both systemic and locoregional; e.g., TACE, interferon, antiviral therapy) have been proposed, aiming to reduce recurrence following resection with varying success. Studies of these agents have been unsuccessful in demonstrating a consistent improvement in short-term (e.g., disease free survival (DFS) and recurrence free survival (RFS)) and long-term (e.g. OS) clinical endpoints.

In the United States, the guidelines for the treatment of HCC of professional organizations, such as the AASLD, American Gastroenterological Association (AGA), NCCN, and ASCO, do not mention Ta1 in their recommendations (Singal et al. 2023; Su et al. 2022; Rose et al. 2024).[172]

Considerations for Assessing Effectiveness

FDA's guidance for industry, *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*, provides recommendations on endpoints for cancer clinical trials submitted to the FDA to support effectiveness claims in new drug applications (NDAs), biologics license applications (BLAs), or supplemental applications.[173, 174] In terms of clinical trial designs, the

[171] TACE is the intraarterial infusion of cytotoxic agents and subsequent embolization of the artery to the tumor (https://www.ncbi.nlm.nih.gov/books/NBK559177/). TACE leverages the arterial blood supply of HCC, compared with portal venous blood flow to the background liver, and can be performed with lipiodol (conventional TACE) or drug eluding beads (DEB-TACE).

[172] For the NCCN Guidelines on HCC (version 2.2024), see https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1514.

[173] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-cancer-drugs-and-biologics. Accessed May 14, 2024.

[174] We note that compounded drug products are not subject to the approval or licensure standards discussed in this guidance; however the information in the guidance regarding measuring clinical outcomes helps to inform FDA's consideration and evaluation of the clinical data on the effectiveness of Ta1 for use in treating HCC.

guidance states that single-arm trials do not adequately characterize time-to-event endpoints such as OS and DFS, among others. Because of the variability in the natural history of many forms of cancer, a randomized, controlled study is necessary to evaluate time-to-event endpoints. The definitions of two endpoints are provided below.

OS is defined as the time from randomization until death from any cause and is measured in the ITT population. Survival is considered the most reliable cancer endpoint. The guidance for Industry, *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologic* also notes,

> Overall survival should be evaluated in randomized controlled studies. Data derived from externally controlled trials are seldom reliable for time-to-event endpoints, including overall survival. Apparent differences in outcome between external controls and current treatment groups can arise from differences other than drug treatment, including patient selection, improved imaging techniques, or improved supportive care. Randomized studies minimize the effect of these known and unknown differences by providing a direct outcome comparison.[175]

DFS is defined as the time from randomization until disease recurrence or death from any cause. DFS is also known as relapse-free survival and RFS, and it is based on tumor assessments. The most frequent use of this endpoint is in the adjuvant setting after definitive surgery or radiotherapy. For tumor related endpoints, FDA recommends that tumor assessments generally be verified by central reviewers blinded to study treatments to ascertain lack of assessment bias.

a. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

We identified eight studies using Ta1 in patients with HCC.[176] These studies are summarized in Appendix 2 and are organized chronologically. Six studies were conducted in China, one in Italy, and one in the United States. All but one (Gish et al. 2009) were single center studies. We identified four retrospective studies (He et al. 2017; Liang et al. 2016; Linye et al. 2021; Zhou et al. 2018), one single arm study with a historical control (Stefanini et al. 1998), one non-randomized controlled trial (Cheng et al. 2005), and two RCTs (Gish et al. 2009; Cheng et al. 2004).

In six of the studies, Ta1 was administered as a SC injection at a dose of 1.6 mg (or the approximate equivalent BSA dose of 900 $\mu g/m^2$) twice a week (BIW) for 6 months. One study

[175] See: Guidance for Industry *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologic* at 7, accessed 5/16/24, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-cancer-drugs-and-biologics.

[176] We considered publicly available articles with the full text article in English. We did not consider meeting or conference abstracts. We identified one protocol announcement for a multicenter RCT in China (Qiu et al. 2015); however, we did not identify a corresponding article with results. We identified one article available as a pre-print article (Anti-PD-1 antibody therapy combined with thymosin alpha-1 improves the postoperative prognosis in patients with hepatocellular carcinoma after hepatectomy: a prospective cohort study); however, we did not identify a corresponding publication in an academic journal. Pre-prints are generally preliminary versions of scientific manuscripts before peer-review and publication in an academic journal. In studies with overlapping populations, we only included the most recent article or the article reporting on the largest number of subjects.

(Gish et al. 2009) administered Ta1 five times a week for 6 months. The studies reported on endpoints such as OS and RFS, in addition to multiple other endpoints.

Below we describe some of the findings by the setting in which Ta1 was studied:

1) After hepatectomy as an adjuvant therapy to reduce HCC recurrence (Cheng et al. 2005; He et al. 2017; Liang et al. 2016; Linye et al. 2021)

Three of the four studies evaluating Ta1 as adjuvant therapy post hepatectomy were retrospective analyses. The authors generally reported beneficial effects in this setting. For example, the retrospective study by Liang et al. (2016) reported the 1-, 2- and 3-year OS rates of 87.2, 82.0 and 68.4% in the Ta1 group and 78.2, 64.2 and 49.7% in the historical control group. However, retrospective studies such as these have significant limitations. Data collected retrospectively are confounded by other factors and it is not possible to attribute a difference to the causal relationship of treatment-outcome. This limitation is only partially addressed by adjusting for patient characteristics or applying propensity score matching because it is not possible to control for unknown, unmeasurable, or unmeasured factors.

Cheng et al. (2005) was a small, prospective non-randomized study in which patients with HCC and CHB were treated with hepatectomy only or with Ta1 for 6 months in combination with lamivudine for two years after hepatectomy. Because of the study design, it is not possible to determine the contribution of or necessity for Ta1 for the treatment effect because patients received concurrent lamivudine. In addition, the small treatment cohorts, conduct of the study at a single center, and CHB in all patients enrolled in the study limit the interpretability and the generalizability of the results.

2) With TACE (Gish et al. 2009; Stefanini et al. 1998)

Stefanini et al. (1998) was a single arm study in 12 patients with HCC who received TACE and Ta1 for 6 months. These patients were compared to a historical control group of 12 patients with HCC who had been previously treated with TACE. The authors concluded that the combination of Ta1 and TACE prolonged survival. However, because of the very small sample size and the single arm design, time-to-event endpoints, like OS, cannot be interpreted. In addition, there are limitations inherent to single center studies and the methods used to retrospectively identify matched controls. Other endpoints (e.g. increase in CD16+ and CD56+ cells, or reduction in CD25+ cells) were exploratory and have not been validated as early or intermediate endpoints associated with disease prognosis or the anti-tumor effect of the investigational regimen.

Gish et al. (2009) conducted a phase 2, R pilot study in 25 patients with unresectable HCC who received TACE plus Ta1 (n=14) or TACE alone (n=11) for 24 weeks. Per the authors, Ta1 was added to TACE to increase tumor response and survival time compared with treatment with TACE alone. There was no difference in the "response rate" (defined as transition to transplant eligibility or lack of disease progression through week 72) or in median OS between the treatment and control groups. Gish et al. (2009) was designed primarily as a safety study and therefore was not powered for efficacy outcomes. Gish et al. (2009) recognized the need for a larger, phase 3 trial to evaluate the Ta1 and TACE regimen.

3) After hepatectomy and with TACE to reduce recurrence (Cheng et al. 2004)

Cheng et al. (2004) conducted a single center RCT in 57 patients with HCC who received hepatectomy plus TACE and Ta1 postoperatively (group A; n=18), hepatectomy plus TACE postoperatively (group B; n=23), or hepatectomy only (group C; n=16). There was no difference in the 1-year "recurrent rate" (defined as two of three imaging checks indicating new growth of the tumor at 1 year). The authors did, however, state that there was a difference in the recurrent time (7.0, 5.0, and 4.0 months, respectively, in groups A, B, and C) and the median OS (10.0, 7.0, and 8.0 months, respectively, in groups A, B, and C). The authors provided limited details on the study design and statistical analysis. Upon reanalysis of the data from this study, a Cochrane Review (Wolf et al. 2011) did not find a statistically significant difference in OS or DFS. In addition, the review categorized this study as having a "high risk of bias" for OS and DFS outcomes. Patients were "randomly divided into three groups based on the date of admission." In addition, blinding was not reported and there was an imbalance in disease stage; the proportion of patients with Stage IV was higher in the Ta1 group.

4) After liver transplantation to decrease HCC recurrence (Zhou et al. 2018)

Zhou et al. (2018) performed a retrospective study of 36 patients with advanced HCC who did not meet the University of California at San Francisco (UCSF) criteria for liver transplantation but who underwent liver transplantation at the Organ Transplant Institute of the Chinese PLA 309th Hospital between January 2008 and January 2014.[177] Patients were treated with sirolimus based therapy, Ta1, and huaier granules (n=18) or tacrolimus-based therapy (n=18) after liver transplantation. It is not possible to determine the contribution of Ta1 from this study because patients were also receiving sirolimus and huaier granules.[178]

In summary, these studies do not provide evidence that Ta1 contributes to a clinical response in patients with HCC. The studies showing potential beneficial effects of Ta1 were conducted retrospectively, enrolled a very small number of patients, were not adequately designed to assess the study endpoints (e.g. analysis of OS in single arm trials or using descriptive statistics), and in some studies, patients received other therapy in combination with Ta1 when the studies were not designed to demonstrate the contribution of Ta1. In the two small RCTs identified to date, there was no difference in the 1-year "recurrent rate" (defined as two of three imaging checks indicating new growth of the tumor at 1 year) (Cheng et al. 2004), "response rate" (defined as transition to transplant eligibility or lack of disease progression through week 72), or median OS (Gish et al. 2009) between the treatment and control groups. Of note, these studies are geographically limited, and their results may not be directly applicable to patients in the United States because of substantial epidemiological differences. For example, due to differences in prevalence of HBV and in the age and gender of patients with HBV in Eastern and Western countries, the applicability of the results may be limited to countries with similar epidemiological and transmission dynamics to China.

[177] The UCSF criteria is a single lesion ≤6.5 cm or ≤3 lesions with the largest being ≤4.5 cm and a total diameter ≤8 cm. See https://www.ncbi.nlm.nih.gov/books/NBK569804/table/Ch7-t0001/.
[178] According to authors huaier granules are a type of traditional Chinese medicine.

As noted above, FDA generally recommends randomized trials for time-to-event endpoints such as OS and DFS due to the variability in the natural history of many forms of cancer. In addition, FDA recommends that tumor assessments be verified by central reviewers blinded to study treatments to ascertain lack of assessment bias. Potential limitations with non-randomized studies include selection bias and confounding. A recent special communication article in *JAMA Oncology* discussing the use of single arm trials in oncology approval, states that time-to-event points such as OS necessitate a randomized trial due to their sensitivity to baseline differences in patient, disease, and other clinical characteristics (Agrawal et al. 2023).

Other Studies

The protocol announcement from Qui et al. (2015) summarizes the potential beneficial effects of Ta1 in the four prospective studies discussed above (Cheng et al. 2005; Gish et al. 2009; Cheng et al. 2004; Stefanini et al. 1998). Qui et al. (2015) recognized that there has been no large-scale RCT in resectable HCC patients and proposed the following: "To confirm the role of thymalfasin adjuvant therapy in patients with HBV-related HCC after curative resection, a large-scale, multicenter, RCT has been planned in China, to investigate the effect of thymalfasin (1.6 mg twice a week for 12 months) on 2-year RFS rate and tumor immune microenvironment." We have not identified results from this study to date. However, considering the geographic prevalence of HBV-associated HCC and data suggesting better clinical outcomes in this population of patients, the generalizability of the results of these studies to a US population may be limited.

As discussed in Section II.D.6, we identified a Cochrane Review that evaluated the effectiveness of purified thymus extracts (thymostimulin or thymosin fraction 5) and synthetic thymic peptides (thymopentin or Ta1) for the management of cancer (Wolf et al. 2011). The authors identified 26 RCTs that met their inclusion criteria; four of which used Ta1 (Gish et al. 2009; Maio et al. 2010; Schulof et al. 1985; Cheng et al. 2004). For Ta1, the pooled RR for OS was 1.21 (95% CI 0.94 to 1.56, P = 0.14), with low heterogeneity; and 3.37 (95% CI 0.66 to 17.30, P = 0.15) for DFS, with moderate heterogeneity. This was a pooled analysis of studies in multiple cancer types. Although the authors concluded that there were trends towards reduced risks of death and disease recurrence with Ta1, statistical significance was not achieved and several of the studies were deemed to be at moderate or high risk of bias.

b. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

HCC is serious and life-threatening.

c. Therapies that have been used for the condition(s) under consideration

There are not FDA-approved drug products that treat the same medical condition as that proposed for the Ta1 compounded drug product in the adjuvant setting; however, there are FDA-approved drug products that treat the same medical condition as that proposed for the Ta1

compounded drug in patients with unresectable HCC. The NCI maintains a list of currently available FDA-approved drug products indicated for liver cancer, including HCC.[179]

d. Conclusion

There is insufficient evidence to demonstrate the effectiveness of Ta1 as a treatment option for HCC, which is a serious disease. In the two RCTs identified to date, there was no difference in the 1-year "recurrent rate" (Cheng et al. 2004) or "response rate" and median OS (Gish et al. 2009) between the treatment group that received Ta1 and the control group. Several retrospective studies reported beneficial effects of Ta1 in the adjuvant setting after hepatectomy. However, due to the limitations in the study designs it is unclear what, if any, contribution Ta1 provided. There are no FDA-approved drug products for HCC in the adjuvant setting; however, there are FDA-approved drug products for the treatment of unresectable HCC.

8. Non-small cell lung cancer (NSCLC)

Lung cancer accounts for approximately 12% of all new cancers and it is the leading cause of cancer deaths, accounting for about 20% of all cancer deaths.[180] While lung cancer survival rates are improving, overall prognosis remains poor with a 5-year survival rate of approximately 27% in the US. NSCLC is the most common type of lung cancer accounting for approximately 85% of the cases worldwide. The WHO classified NSCLC into three main histologic types: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (Duma et al. 2019). Tumor staging per the 8th edition of American Joint Committee on Cancer (AJCC) lung cancer classification is based on the tumor-node-metastasis (TNM) descriptors (Alexander et al. 2020).

Treatment approaches in NSCLC include surgery, radiotherapy, chemotherapy, immunotherapy, and targeted therapy either alone or in combination depending on the stage, histology, genetic alterations, and the patient's condition.[181] Current standard of care for patients with locally advanced NSCLC (LA-NSCLC) who are eligible for radiation therapy is complex and frequently includes concurrent chemotherapy and adjuvant immunotherapy (Antonia et al. 2017). In the United States, clinical practice guidelines for management of patients with NSCLC are available from the NCCN[182] (Riely et al. 2024). These NCCN guidelines do not include Ta1 as a recommended treatment for patients with NSCLC.

a. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

[179] See NIH National Cancer Institute at https://www.cancer.gov/about-cancer/treatment/drugs/liver. Accessed June 13, 2024.
[180] See National Cancer Institute cancer statistics from Surveillance, Epidemiology, and End Results (SEER) program for lung and bronchus cancer NSCLC https://seer.cancer.gov/statfacts/html/lungb.html (accessed June 11, 2024)
[181] See American Cancer Society treatment choices for NSCLC, by stage https://www.cancer.org/cancer/types/lung-cancer/treating-non-small-cell/by-stage.html (last accessed June 11, 2024).
[182] The NCCN is a not-for-profit alliance of 33 leading cancer centers devoted to patient care, research, and education. NCCN programs offer access to expert physicians, superior treatment, and quality and safety initiatives that continuously improve the effectiveness and efficiency of cancer care globally.

The nomination for Ta1 proposes its use both in NSCLC and as a chemotherapy adjunct. The NCI defines **adjunct** therapy as another treatment used together with the primary treatment; its purpose is to assist the primary treatment.[183] Therefore, studies that evaluated Ta1 when used as chemotherapy adjunct will need to demonstrate whether Ta1, which is not routinely utilized in the management of NSCLC, provides clinical benefit when used in conjunction with chemotherapy that is routinely used for management of NSCLC.

For the evaluation of data on effectiveness of Ta1 in NSCLC, we considered data from eight articles that are summarized below.

Schulof et al. 1985: This single center[184] R, DB, PC prospective study investigated whether Ta1 used as monotherapy exhibited an immunomodulatory effect in 42 patients with unresectable LA-NSCLC who were considered eligible for radiation therapy because their cancers were not resectable or because all disease could not be removed at thoracotomy. The immunomodulatory effect in this study population was characterized by changes in absolute T cell counts and any changes in T cell function in lymphoproliferative assays. Additionally, the study evaluated differences in outcomes on survival in patients who were on two different Ta1 dosing schedules (Groups II and III) compared to a placebo group (Group I). The authors noted that the study was not designed to determine effectiveness based on survival outcomes.

Ta1 (900 µg/m^2) was administered SC as monotherapy in 14 patients each in Groups II and III and was compared to placebo (Group I; n=13).[185] Patients receiving Ta1 were administered either twice weekly dosing (Group II) or a Ta1 daily loading dose for 14 days and then twice weekly maintenance thereafter (Group III). To maintain study blinding, all patients in Group I and Group II began with 14 daily injections with placebo, while the patients in Group III received daily Ta1 loading doses for 14 days. Patients received investigational products for up to 1 year or until relapse or death. Hoffman-La Roche (USA) provided the study drugs.

Although the primary objective was "to determine whether the administration of synthetic Ta1 by either a loading dose or a twice-weekly schedule could accelerate the reconstitution of thymic dependent immunity" and therefore assess Ta1's immunomodulatory effect, the clinical meaningfulness of various assessments of T cell function in patients with NSCLC is unknown. Furthermore, in this setting these endpoints are not considered surrogate or early clinical endpoints that are reasonably likely to predict clinical benefit. As the relationship of these endpoints to direct measures of clinical benefit is unknown, these assessments are considered exploratory.

Considering the current standard of care for patients with LA-NSCLC some patients with molecular or genetic alterations may be candidates for targeted therapy. The stage and genetic subtype of patients in this study per contemporary classifications is unknown.

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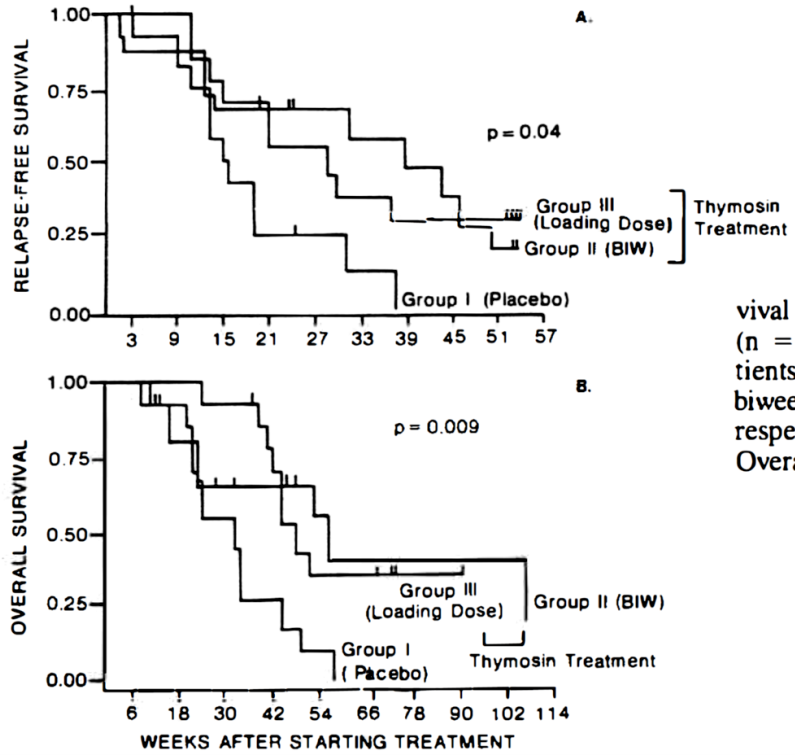
[183] See NCI definition for adjunct therapy https://www.cancer.gov/search/results?swKeyword=adjunct+therapy. Accessed 05/14/2024.

[184] George Washington University Medical Center, USA

[185] Patients were eligible for primary radiation therapy because their cancers were not considered surgically resectable or because all disease could not be removed at thoracotomy. Eligible patients did not have evidence of metastatic disease on bone and liver spleen scans, and no prior or concurrent chemotherapy, immunotherapy, or steroids and with normal hepatic and renal function.

Patients were followed until death, with a median follow-up time of 40 weeks (range 8-108 weeks). Figure 10 shows OS and relapse-free Kaplan-Meier survival estimates for each study arm. Although the study was not designed to measure effectiveness, the study reported showing improvements in both relapse-free survival and OS for the two Ta1-treated groups when compared with the placebo group. There was no difference in OS between Ta1 dosing regimens in Groups II and III.

Figure 10. Kaplan-Meier OS and Relapse-free Survival Estimates for Ta1 Groups II and III compared to Placebo Group I (Schulof et al. 1984).



Kaplan-Meier actuarial survival estimates for all evaluable patients (n = 41), including 13, 15, and 13 patients in Groups I (placebo), II (thymosin biweekly), and III (thymosin loading dose), respectively. **A**: Relapse-free survival. **B**: Overall survival.

Source: Schulof RS. et al. 1984. Modified Figure 3. A: Relapse-free survival. B: Overall survival.

We agree with the authors conclusions that "because of the small patient numbers involved in our trial and the prognostic imbalances among the groups, our results must be interpreted cautiously. Definitive conclusions regarding the impact of thymosin therapy on survival can only be ascertained in large-scale multi-institutional trials."

Dillman et al. 1987: This single center[186] OL study evaluated two types of thymosin peptides separately: Ta1 and thymopentin[187] (thymosin fraction 5 (TF5); another thymosin derivative five amino acid peptide) in patients with different types of cancers, to evaluate the investigational drugs' "antitumor" and "immune-modulating effects." Patients with advanced malignancy who

[186] University of California San Diego, La Jolla, CA. The clinical trial was supported with grant through the Biological Response Modifiers Program of the National Cancer Institute and American Cancer Institute.
[187] See NCI drug dictionary for thymopentin https://www.cancer.gov/publications/dictionaries/cancer-drug/def/thymopentin. Accessed 06/11/2024).

had disease progression after standard therapies were enrolled. Hoffman-La Roche (USA) provided the investigation study drugs. Corticosteroids and immunosuppressive agents were prohibited.

- Ta1 1.2 mg/m^2 IM three times weekly (during weeks of concurrent chemotherapy) for at least one month was evaluated in ten patients with advanced NSCLC who "failed standard effective therapies and recovered from side effects of previous treatments" for NSCLC. The study evaluated Ta1 used as "immunostimulant" to produce antitumor effects by itself or whether Ta1 'immunomodulates" the anticancer effects of cytotoxic agents. Other participants who received Ta1 included: five with renal cell cancer, and one with thymoma.
- TF5 120 mg/m^2 three times weekly was administered to the following groups:12 patients with colon cancer, 3 with hypernephroma[188], 1 with hepatoma, and 1 with thymoma.

The authors reported that there were no "tumor responses" or "immunomodulating effects." Assessments for Ta1 with concurrent chemotherapy appeared to have been based on immunology data compared to age matched healthy (normal) controls. The authors reported that NCI-sponsored trials under the Biological Response Modifier conducted in other centers also failed to show antitumor effects in advanced NSCLC for Ta1. They concluded that "it is apparent that TF5 and Ta1 have no role to play in advanced cancer as single agents. In the absence of more convincing evidence of immune augmentation, it is not clear that large-scale adjuvant trials or combination chemotherapy-immuno-therapy trials are warranted with these hormones."

Garaci et al. 1995: This OL single arm study evaluated the clinical and immunological effects of chemotherapy in addition to interferon-alpha 2a (IFN-alpha) concomitantly administered with Ta1 in 56 patients with advanced Stage III and IV NSCLC. Of the study participants, 46 did not receive prior chemotherapy. Ta1 was hypothesized to enhance immune response of chemotherapy with IFN and cisplatin-containing combinations in NSCLC.

Patients received concomitant chemotherapy that consisted of cisplatin (100 mg/m^2 administered on day 1 as a 2 h IV infusion with fluid loading) and VP-16 (120 mg/m^2 IV on days 1-3) combined with Ta1 (1 mg SC on days 8-11 and 5-18), and recombinant low-dose IFN (3 MU SC on days 11 and 18, 1-hour after Ta1 injection). Cycles were repeated every 3 weeks according to hematological and renal status. Tumor response was assessed after two cycles. Patients were given a maximum of six cycles until disease progression or major toxicity. Sclavo (Siena, Italy) provided Ta1 in lyophilized vials containing 2 mg/vial.

Based on the single-arm study design where several drugs were administered concomitantly, it is not possible to determine the contribution of Ta1 administration to the overall treatment effect of the regimen. Therefore, discussion of the results is not included.

Salvati et al. 1996: This OL, R study evaluated patients with stage III and IV NSCLC without previous treatment who were administered ifosfamide chemotherapy 3 g/m^2 IV (n=10) compared to patients who were concomitantly administered ifosfamide followed by Ta1 1 mg SC with low dose IFN (n=12). Ta1 was administered to enhance the immune response of chemotherapy with IFN. The authors stated that Ta1 and IFN were administered together because they were shown

[188] Hypernephroma is commonly referred to as renal cell carcinoma.

to be not effective as single agents in NSCLC. Sclavo (Siena, Italy) provided Ta1 in lyophilized vials containing 2 mg/vial.

Median overall survival in the ifosfamide alone arm was 16 weeks (range 11-63) and in the concomitant chemotherapy+Ta1+IFN arm was 24 weeks (range 14-67). Results of statistical analyses of overall survival were not reported. Based on the two-arm study design where several drugs were administered concomitantly, it is not possible to determine the contribution of Ta1 administration to the overall treatment effect of the regimen. Therefore, further discussion of the results is not included.

Guo et al. 2021: This retrospective study evaluated Ta1 injections administered postoperatively as monotherapy or in combination with several other adjuvant treatments in 1027 patients with stage IA-IIIA NSCLC.[189] Patient who received Ta1 either as a monotherapy (67%) or in combination with other adjuvant therapies[190] were compared to a propensity score matched (PSM) control group (n=1027 where Ta1 was not administered).[191]

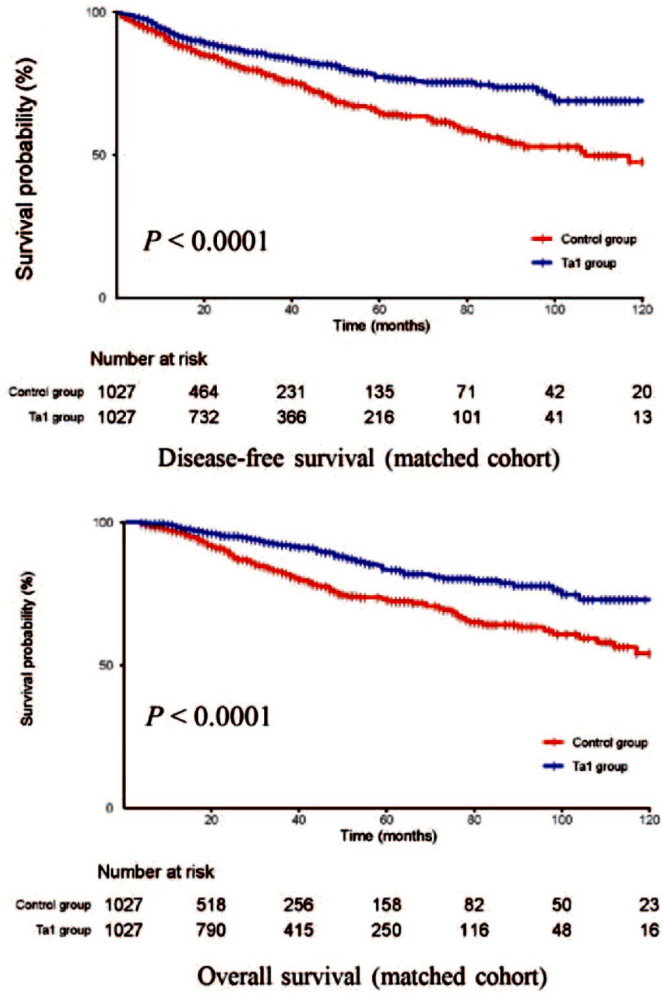
Propensity score matching identified 1027 qualifying patients in the control group from an initial group of 4719 patients from the Western China Lung Cancer Database (WCLCD) in West China Hospital, Sichuan University who underwent complete surgical resection for primary NSCLC[192] between May 2005 and December 2018.[193] Patients in both the study and PSM group did not receive immune checkpoint inhibitors.

Ta1 1.6 mg SC was administered twice weekly 1 to 3 months after surgery with the doses every 3 to 4 days. The study evaluated long-term survival outcomes measured by OS and DFS in the retrospective analysis in PSM-matched NSCLC patients. Patients in the Ta1 group were further divided into three groups based on treatment duration with Ta1: < 12 months (n = 375), 12 to 24 months (n = 282), and >24 months (n = 370) to investigate the effect of the duration of Ta1 on the long-term outcomes. OS was calculated as the time from surgery until death from any cause or last follow-up. DFS was defined as the period from the surgery date until any local or distant recurrence or death or last follow-up.

The authors concluded that Ta1 as adjuvant therapy (i.e., Ta1 combined with other adjuvant treatments) could delay tumor recurrence and prolong OS in patients with stage I–III NSCLC following margin-free resection. The retrospective study reported higher 5-year DFS (77.3% vs. 64.7%) and OS rates (83.3% vs. 72.7%) in the Ta1 (overall any adjuvant therapy) group compared with the control group (Figure 11).

[189] NSCLC stage I (early) including stage II and IIIA (locally advanced after R0 (margin free) resection surgery).
[190] In the Ta1 group, 692 of 1027 subjects (i.e., 67%) were postoperatively treated with Ta1 alone, 164 (16%) with Ta1 combined with chemotherapy, 58 (5.6%) Ta1 combined with targeted therapy, 51 (5%) Ta1 combined with chemoradiotherapy, 27 (2.6%) Ta1 combined with chemotherapy plus targeted therapy, and 35 (3.4%) Ta1 combined with chemoradiotherapy plus targeted therapy.
[191] Among the PSM control group (i.e., no Ta1 treatment group), 67%, 16%, 5.4%, 6%, 2.4, and 3% patients received chemotherapy, targeted therapy, chemoradiotherapy, chemotherapy plus targeted therapy, and chemoradiotherapy plus targeted therapy after surgery, respectively.
[192] NSCLC was staged according to the seventh edition of the American Joint Committee on Cancer (AJCC) TNM staging system for lung cancer.
[193] To minimize selection bias between two groups, propensity score matching (PSM) was performed using R (version 3.5.2, R Core Team, 2018) and the MatchIt package (author cited reference from Daniel Ho, 2018).

Figure 11. Kaplan–Meier curves for DFS and OS of patients between the Ta1 group and control group in PSM cohort (Guo et al. 2021).



Source: Guo et al. 2021. Modified Figure 2.

We agree with the authors conclusions noting the limitations of the retrospective study design and that these data are hypothesis generating and do not support the effectiveness of Ta1 as adjuvant therapy for resectable NSCLC either alone or in combination with other drugs.

The authors additionally note that "First, although we attempted to balance the variables between the two groups using PSM, selection bias and unobserved confounding associated with the retrospective nature of the study cannot be eliminated. Second, the generalization of the observed outcomes in the subgroup analyses to clinical practice must be cautiously scrutinized because the sample size for some subsets in this series was small. Third, the Eastern Cooperative Oncology Group's[194] performance status was missing in most patients. Finally, the data were derived from

[194] See https://ecog-acrin.org/resources/ecog-performance-status/. The ECOG-ACRIN Cancer Research Group is a strong network of nearly 1300 academic and community-based cancer centers and hospitals in the United States and around the world.

a single institution. Thus, more studies from other institutions, preferably multicenter studies, are encouraged to validate our results."

Zeng et al. 2019: This systematic review and meta-analysis[195] of clinical trials conducted exclusively in China evaluated data for two types of thymosin peptides: Ta1 and TF5. In the selected trials, patients with unresectable stage IIIa and IV NSCLC, received either Ta1 or TF5 used in combination with chemotherapy[196] to determine whether these thymosin peptides improved tumor response and patient survival compared to a chemotherapy alone control group.

Twenty-seven RCTs included 1925 patients when both peptides were considered. Table 8 shows information that is highlighted with study characteristics for Ta1 treated subjects in 19 studies including 1333 patients.[197] Ta1 or thymopentin used in combination with chemotherapeutic treatments was administered in 976 cases, and 949 cases received chemotherapy alone.

[195] The analysis was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines https://www.prisma-statement.org/

[196] Chemotherapies included gemcitabine and cisplatin (GP), navelbine and cisplatin (NP), gemcitabine and carboplatin (GC), docetaxel and cisplatin (DP), paclitaxel and cisplatin (TP), taxinol and carboplatin (TC), etoposide and cisplatin (EP), mitomycin, vindesine and cisplatin (MVP) and navelbine, ifosfamide and cisplatin (NIP).

[197] The authors excluded the following types of studies if: either Ta1 or thymopentin peptides were combined with surgery, radiotherapy, traditional Chinese medicine, or other biological regulators; in vitro/in vivo studies, generic, patents, abstracts, reviews without specific data, and unrelated systematic reviews or meta-analyses; cohort and case control studies, case series, and case reports; and studies without data regarding tumor response, survival, peripheral blood lymphocyte levels, ADRs, or HAIs.

Table 8. Clinical Trials Included in Meta-analysis for Thymosin Peptides: Ta1 and Thymopentin (Zeng et al. 2019).

Characteristics of the included trials.

First author, year	Non-small cell lung cancer (NSCLC)				Interventions		Criteria A, B, C	Follow-ups	Outcomes
	Stages	E/C	M/F	Age	Synthetic thymic peptides (sTPs) (dose/frequency, treatment time/cycle, cycles)	Chemotherapy			
Chen, Y. 2005 [56]	IIIb–IV	23/19	24/18	38–76	Thymopentin: 1 mg/time, 1–2/d, 15d/C, 2–3 cycles (IV)	NP	No/No/FCM	4–6w	O4, O5
Wang, H. 2005 [57]	III–IV	20/20	26/14	26–74	Thymosin α1: 1.6 mg/d, qd, 4d, change to 3/w, 4w/C, 1 cycle (SI)	MVP/NIP	WHO/NCICTC/FCM	3 years	O1–O5
Ma, D. 2006 [58]	III–IV	36/33	42/27	Un	Thymosin α1: 1.6 mg/d, qd, 7d, change to 1/2d, 3w/C, 4 cycles(SI)	NP	WHO/NCICTC/No	4 years	O1, O3
Hou, X. 2007 [59]	IIIb–IV	34/34	49/19	33–69	Thymosin α1: 1.6 mg/time, 2/w, 3w/C, 3–4 cycles(SI)	NP	WHO/Unclear/No	12w	O1, O2, O3
Shi, X. 2007 [60]	III–IV	29/29	49/9	36–69	Thymosin α1: 1.6 mg/time, 1/2d, 6w/C, 1 cycle (SI)	NP	WHO/WHO/FCM	6w	O1, O4–5
Zhen, J. 2008 [63]	Advanced	28/26	38/16	43–79	Thymosin α1: 1.6 mg/time, 2/w, 10d/C, 3–4 cycles (SI)	NP	WHO/WHO/No	12–16w	O1–2, O4
Liu, P. 2008 [61]	IIIa–IV	32/32	44/20	38–73	Thymopentin: 1 mg/time, qd, 4w/C, 2 cycles (IM)	NP	No/No/FCM	8w	O5
Wu, L. 2008 [62]	Advanced	16/15	19/12	Un	Thymosin α1: 1.6 mg/time, 3/w, 6w/C, 1 cycle (SI)	GP	No/No/Unclear	6w	O5
Lin, F. 2009 [64]	III–IV	100/100	162/38	36–69	Thymopentin: 10 mg/d, qd, 7–10d/C, 2 cycles (IV)	GP	WHO/WHO/Un	Un	O1, O5
Sun, X. 2009 [65]	III–IV	34/34	47/21	34–69	Thymosin α1: 1.6 mg/d, qd, 21d/C, 1 cycle (SI)	GC	No/No/FCM, MTT	3w	O5
Liang, B. 2010 [22]	IIIb–IV	30/28	39/19	65–75	Thymosin α1: 1.6 mg/time, 1/2d, 8w/C, 1 cycle (SI)	Gem	WHO/WHO/No	Un	O1, O4
Zhou, Z. 2010 [67]	IIIb–IV	33/35	51/17	Un	Thymopentin: 1.0 mg/time, 3/w, 4w/C, 3 cycles (SI)	EP	WHO/WHO/No	Un	O1, O4
Gu, Y. 2010 [66]	IV	29/29	30/28	40–75	Thymosin α1: 1.6 mg/d, qd, 4d, change to 2/w, 8w/C, 1 cycle (SI)	GP/DP	No/No/IIT, LDH	8w	O5
Han, L. 2012 [68]	IIIb–IV	32/32	42/22	42–68	Thymosin α1: 1.6 mg/time, 1/2d, 9w/C, 1 cycles (SI)	NP	WHO/WHO/FCM	Un	O1, O4–5
Li, W. 2012 [69]	III–IV	36/28	52/12	36–70	Thymosin α1: 1.6 mg/time, 3/w, 3–4w/C, 2 cycles (SI)	TP	WHO/WHO/No	6–8w	O1, O4
Liu, Y. 2012 [70]	III–IV	45/45	49/41	55–72	Thymosin α1: 1.6 mg/time, 2/w, 4w/C, 1 cycle (SI)	DP	RECIST/WHO/FCM	12w	O1, O4–5
Wang, Y. 2012 [71]	III–IV	30/30	47/13	40–74	Thymosin α1: 1.6 mg/time, 2/w, 3–6 M/C, 1 cycle (SI)	NP, TP, GP	WHO/WHO/FCM	4w	O1–5
Shui, H. 2014 [73]	IIIb–IV	24/25	31/18	43–76	Thymosin α1: 1.6 mg/time, 1/2d, 3w/C, 2 cycles (SI)	GP	RECIST/No/Unclear	Un	O1, O5
Zhao, M. 2014 [74]	IIIb–IV	52/48	59/41	32–68	Thymosin α1: 1.6 mg/time, 1/2d, 2w/C, 2–4 cycles (SI)	TP, NP, GP	No/No/FCM	1 year	O3–5
Cai, P. 2014 [72]	III–IV	40/38	50/28	42–76	Thymosin α1: 1.6 mg/time, 2/w, 6–8w/C, 1 cycle (SI)	NP	No/No/FCM	6w	O5
Chen, Q. 2015 [75]	Advanced	28/28	38/18	40–74	Thymopentin: 1 mg/d, qd, 7d/C, 2 cycles (IV)	GC	WHO/WHO/Unclear	Un	O1–2, O4
Mo, Y. 2015 [77]	III–IV	34/34	43/25	39–74	Thymosin α1: 1.6 mg/time, qd, 2 M/C, 1 cycle (SI)	GP	RECIST/No/Unclear	Un	O1, O5
Shao, Z. 2015 [78]	Advanced	32/32	48/16	36–78	Thymopentin: 1 mg/d, qd, 14d, 3w/C, 3 cycles (IV)	TP	WHO/Unclear/No	Un	O1, O4
He, W. 2015 [76]	IIIb–IV	25/25	31/19	70–80	Thymopentin: 1 mg/time, 2/d, 15d/C, 2 cycles (IV)	GP	No/No/FCM	4w	O5
You, L. 2017 [39]	III–IV	100/100	133/67	36–78	Thymosin α1: 1.6 mg/time, 2/w, 3w/C, 1 cycle (SI)	TP, NP, GP	No/WHO/FCM	Un	O4, O5
Mao, S. 2017 [38]	IIIb–IV	30/26	32/24	65–80	Thymosin α1: 1.6 mg/time, qd, 7–10d/C, 2 cycle (SI)	Pemetrexed	WHO/WHO/FCM	6w	O1–2, O4–5
Li, L. 2018 [40]	IIIb–IV	24/24	31/17	37–70	Thymopentin: 10 mg/time, 2/w, 14d/C, 2 cycles (IV)	TC	WHO	6–8w	O2, O4

Note: E/C: experimental group (synthetic thymic peptides with chemotherapy)/Control group (chemotherapy alone), M/F: male/female, SI: subcutaneous injection, IV: intravenous injection, IM: intramuscular injection, DP: docetaxel and cisplatin, EP: etoposide and cisplatin, NP: navelbine and cisplatin, MVP: mitomycin, vindesine and cisplatin, NIP: navelbine, ifosfamide and cisplatin, GP: gemcitabine and cisplatin, TP: taxinol and cisplatin, TC: taxinol and carboplatin, Gem: gemcitabine, GC: gemcitabine and carboplatin, Criteria.A: evaluation criteria of tumor response, Criteria.B: evaluation criteria of ADRs, RECIST: response evaluation criteria in solid tumors, CTCAE: Common Terminology Criteria for Adverse Events, Criteria.C: test methods of peripheral blood lymphocytes, FCM: flow cytometry, IIT: indirect immunofluorescence test, LDH: lactic dehydrogenase release. MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. O: Outcomes, O1: ORR and DCR, O2: QOL, O3: survival, O4: ADRs, O5: peripheral blood lymphocyte level.

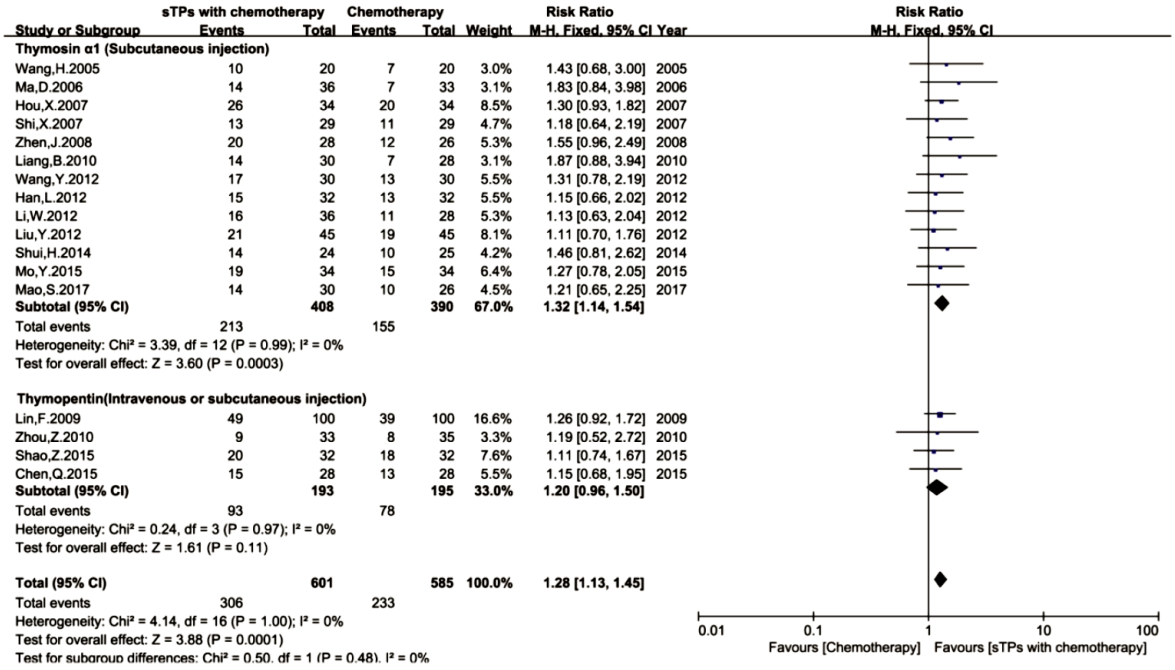
Source: Zeng et al. 2019. Modified Table 1.

Ta1 (1.6 mg) was administered SC across a variety of dosing schedules.

The outcomes reported included tumor response, survival, quality of life (QOL), peripheral blood lymphocyte levels, AEs, and hospital-acquired infections (HAIs). Tumor responses were reported according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Survival endpoints included OS and progression-free survival (PFS).

The meta-analysis presented data for tumor responses from 17 trials including 1186 patients for both thymosin peptides: Ta1 and TF5. The authors reported that compared with chemotherapy alone, administration of Ta1 or TF5 via SC injection with chemotherapy resulted in improvement in overall response rate (ORR) (HR: 1.28, 95% confidence interval [CI]: 1.13, 1.45) (Figure 12). Although not shown here, based on the observations included in trials that recorded data, in-text Figure 4 and 5 in the publication suggested that Ta1 in combination with chemotherapeutic treatments showed improved outcomes for QOL and 1-year OS rate. However, the authors reported that the 1-year OS rate results were not robust and of very low quality. The 2-, 3-, and 4-year OS rates showed no differences between the two groups. Overall, the authors reported that the quality of evidence was moderate for ORR, DCR, QOL, and very low for 1-, 2-, 3-, and 4-year OS rates. In addition to these equivocal findings, this meta-analysis included patients with a variety of tumor stages and tumor histologies, irrespective of genomic alterations, who may be candidates to a variety of contemporary available therapies. It is unclear whether these studies included control arms that are representative of U.S. standards of care or populations.[198]

Figure 12. The Analysis of Tumor Response (ORR) in Advanced NSCLC on Thymosin Peptides: Ta1 or Thymopentin with or without Chemotherapy (Zeng et al. 2019).



[198] It is unclear whether these studies in the meta-analysis included populations representative of U.S. populations and whether the control arms that were included were representative of U.S. standards of care.

Source: Zeng et al. 2019. Supplementary material 3. Subgroup analysis results of ORR (Fig.S7-16).

Jiang et al. 2011: This systematic review and meta-analysis of trials conducted exclusively in China evaluated the efficacy and safety of two types of thymosin peptides: Ta1 and TF5 when administered in combination with either platinum-based doublet chemotherapy (cisplatin with vinorelbine (NP) or gemcitabine with cisplatin (GP)) compared to chemotherapy alone in patients with unresectable stage III and IV NSCLC. Platinum-based doublets chemotherapy was considered the standard treatment scheme for patients with NSCLC at the time of the publication in 2011; however, this is no longer the standard of care for these patients in the U.S. Of note, the studies that were considered in the meta-analysis by Jiang et al. (2011) were also included in the Zeng et al. (2019) meta-analysis discussed earlier. [199]

Although ten RCTs included 724 patients when both peptides (Ta1 and TF5) were considered, five studies included treatment with Ta1 including 320 patients (Table 9 highlighted studies). Ta1 (1.6 mg) was administered SC. The publication did not include information on frequency and number of doses administered.

Table 9. Clinical Trials Included in Meta-analysis for Thymosin Peptides: Ta1 and thymopentin (Jiang et al. 2011).

	Thymosin plus NP/GP							Intervention			NP/GP alone
Trials	Sample size		Sex (female : male)		Age (years)		Stages of NSCLC	Karnofsky score	Trial group	Control group	Outcome	Thymosin dose
Gu AQ 2007[13]	21	21	6/15	5/16	60†/61†		III, IV	≥70	Ts+NP	NP	a,b,c,e,f,g	Ts 200mg sc
Hou XR 2007[14]	34	34	19/49		57.5‡		III, IV	62–85	Ta1+NP	NP	a,c,d,e,f	Ta1 1.6mg sc
Liu PH 2008[15]	32	32	20/44		58.4 ± 0.8		III, IV	60–90	Tp+NP	NP	g	Tp 1mg sc
Ma DT 2006[16]	36	33	27/42		61.5‡		III, IV	70–85	Ta1+NP	NP	a,b	Ta1 1.6mg sc
Shi X 2007[17]	28	29	5/23	4/25	57.4†	59.2†	III, IV	≥60	Ta1+NP	NP	a,f,g	Ta1 1.6mg sc
Liang B 2010[18]	30	28	10/20	9/19	66‡	68‡	III, IV	≥60	Ta1+GP	GP	a,c,d,e,g	Ta1 1.6mg sc
Lin F 2009[19]	100	100	21/79	17/83	56.3‡	58.7‡	III, IV	≥60	Ts+GP	GP	a,f,g	Tp 10mg sc
Shen W 2008[20]	28	28	10/18	8/20	52‡	50‡	III, IV	≥60	Ts+GP	GP	a,c,f,g	Ts 200mg sc
Sun XM 2009[21]	34	34	21/47		57‡		III, IV	NR	Ta1+GP	GP	f,g	Ta1 1.6mg sc
Wang WF 2008[22]	21	21	11/31		60†		III, IV	≥70	Ts+GP	GP	a,c,d,e,	Ts 200mg sc

†Median age; ‡Average age. a, effective rate; b, one year survival; c, the quality of life; d, leukopenia; e, thrombocytopenia; f, T lymphocyte subset; g, NK cell; GP, gemcitabine with cisplatin; NP, vinorelbine with cisplatin; NR, not report; NSCLC, non-small-cell lung cancer; sc, Subcutaneous injection; Ta1, thymosin alpha 1; Tp, Thymopentin; Ts, thymosin.

Source: Jiang et al. 2011. Modified Table 1.

Because the meta-analysis did not present data separately for Ta1, our ability to draw conclusions on the efficacy of Ta1 alone is limited; however, as the study by Jiang et al. (2011) included the same studies by Zeng et al. (2019), no additional information is included in this study.

Liu et al. 2022: This prospective single arm study conducted in China evaluated the effectiveness of Ta1 administered after concurrent chemoradiotherapy (CCRT) in 69 patients with locally

[199] Systematic review and meta-analysis by Zeng et al. 2019 included comparisons to additional chemotherapeutic agents: gemcitabine and cisplatin (GP), navelbine and cisplatin (NP), gemcitabine and carboplatin (GC), docetaxel and cisplatin (DP), paclitaxel and cisplatin (TP), taxinol and carboplatin (TC), etoposide and cisplatin (EP), mitomycin, vindesine and cisplatin (MVP) and navelbine, ifosfamide and cisplatin (NIP).

advanced unresectable stage III NSCLC. Patients were compared to a PSM control group (n=69) derived from the databases of two prospective trials who also received CCRT but without Ta1 (NCT02573506 and NCT03900117).

CCRT included hypofractionated radiation therapy (HRT) using intensity modulated radiation therapy (IMRT) and weekly chemotherapy. [200, 201] Ta1 was intended to reduce the risk of radiation pneumonitis (RP)[202] due to CCRT. It is unclear if any patients received consolidative immunotherapy after CCRT.

Ta1 (1.6 mg) was administered SC once a week up to 2 months after completing CCRT. Patients were followed every 3 months during the first 2 years, then every 6 months during the third to fifth years and every year after 5 years until disease progression or death. Endpoints included OS and PFS,[203, 204], incidence of grade 2 or greater RP, pulmonary fibrosis[205] within 12 months after the start of CCRT.

The authors noted a decreased rate of grade 2 or greater RP in the study group (36.2%) compared to the PSM control group (53.6%). We agree with the authors conclusion that there were no significant differences between groups on median OS and PFS (Table 10) with the combination of CCRT and Ta1.

Table 10. Median PFS and OS (in months) (Liu et al. 2022).

	Study Group (CCRT+Ta1) (n=31)	Control Group (CCRT without the administration of Ta1) (n=20)
PFS	14.4 (95% CI, 11.7-17.1)	10.7 (95% CI, 8.8-12.6)
OS	34.8 (95% CI, 15.6-54.0)	28.7 (95% CI, 12.9-44.6)

The authors acknowledged that "the treatment strategies that were applied were not the same as the standard per NCCN[206] guidelines, so the results may not similarly apply in the standard CCRT settings." The study results are further limited by the externally controlled design, which may be affected by measured and unmeasured confounders.

b. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

NSCLC is serious and life-threatening disease.

[200] HRT-IMRT included 51 Gy in 17 daily fractions or 40 Gy in 10 daily fractions to planning gross tumor target volume as the first course followed by a re-evaluation, and those patients without disease progression had an adaptive plan of 15 Gy in 5 daily fractions or 24 Gy in 6 daily fractions as a boost. Gray (Gy) is the unit of ionizing radiation dose in the International System of Units.
[201] Concurrent chemotherapy consisted of weekly docetaxel (25 mg/m^2) and nedaplatin (25 mg/m^2) during RT.
[202] Radiation induced lung injury (RILI) is a common risk of thoracic radiation therapy. There is 20% to 40% risk for grade 2 or above (G≥2) RP.
[203] OS was defined as the start of CCRT to the date of death from any cause or last follow-up.
[204] PFS was determined from the start of CCRT until any local or distant recurrence, or death from any cause or last follow-up.
[205] CTCAE version 5.0 criteria: G1 pulmonary fibrosis was defined as <25% of lung volume associated with hypoxia.
[206] See NCCN Non-Small Cell Lung Cancer guideline here at https://www.nccn.org/guidelines/category_1.

c. Therapies that have been used for the condition(s) under consideration

There are FDA-approved drug products that treat the same medical condition as that proposed for the Ta1 compounded drug product.

The NCI provides a list of currently available FDA-approved drug products indicated for NSCLC.[207]

d. Conclusion

In summary, these studies do not provide evidence that Ta1 contributes to a clinical benefit in patients with NSCLC. Studies evaluating the efficacy of Ta1 in this setting have generally been retrospective or single arm studies, often including heterogenous populations (e.g., different tumor stages, histologies, and genomic alterations) and frequently included backbone treatment regimens that are inconsistent with contemporary U.S. standard of care.

Two small RCTs have been identified evaluating Ta1 in this setting, Schulof et al. 1985 and Salvati et al. 1996, which are nearly 40 and 30 years old, respectively. The ability of these studies to establish the effectiveness of Ta1 in patients with NSCLC is limited by small sample size (n=22 to 42), advances in staging and genetic characterization of NSCLC since these studies were conducted, and changes regarding U.S. standards of care and available therapies across a variety of NSCLC indications that may have been included in these studies. It is unknown what proportion of patients in these studies expressed actionable genomic alterations and may have received clinical benefit from treatment with targeted therapies. Furthermore, the control therapies received (i.e., placebo and chemotherapy plus interferon) are not consistent with U.S. standard of care for patients with NSCLC without actionable genomic alterations. It is unknown whether the addition of Ta1 to contemporary treatment regimens would have resulted in clinical benefit for these patients.

The remaining studies include a retrospective analysis (Guo et al. 2021), two single arm studies (Dillman et al. 1987 and Garaci et al. 1995), a single-arm study with a matched external control (Liu et al. 2022), and two systematic reviews and meta-analyses (Zeng et al. 2019 and Jiang et al. 2011). Interpretation of the single-arm studies is limited by their sample size (n=10 to 56), which is further compromised by mixed patient populations in regard to stage and prior treatments. Patients included in these studies did not receive contemporary U.S. standard of care chemotherapy; therefore, it is unknown whether Ta1 may provide clinical benefit in current settings. Furthermore, without a comparator arm, it is challenging to draw conclusions from these studies. Due to variability in the natural history of NSCLC, time-to-event endpoints in such single-arm studies are uninterpretable.

Clinical benefit of Ta1 in the single-arm study with a matched external control (Liu et al. 2022) is also challenging to interpret. This study was designed to study the effect of Ta1 on the specific toxicity of radiation pneumonitis and evaluation of efficacy outcomes is limited by sample size

[207] See NIH National Cancer Institute at https://www.cancer.gov/about-cancer/treatment/drugs/lung Accessed September 15, 2024.

(n=69) and by inherent limitations of the externally controlled design (e.g., imbalances in measured and unmeasured confounders).

Finally, the two systematic reviews and meta-analyses included overlapping studies and therefore should be viewed as a single analysis. The efficacy meta-analyses in these studies shows mixed results for patients who received Ta1 and TF5; therefore, it is unclear whether patients who received Ta1 specifically derived clinical benefit. Furthermore, patients in the underlying studies did not receive U.S. standard of care, so it remains unknown whether Ta1 may provide clinical benefit in current settings.

Overall, there is insufficient evidence to demonstrate the effectiveness of Ta1 as a treatment option for NSCLC, which is a serious disease. There are several FDA-approved drug products for patients with NSCLC.

9. Sepsis

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone (Singer et al. 2016). Despite medical advances, standardized protocols, and physician awareness, mortality rates from sepsis in the United States are 20 -36%, with approximately 270,000 deaths annually (Gauer et al. 2020). Major risk factors for developing sepsis are age ≥ 65 years, malnutrition, chronic illness, immunosuppression, recent surgery or hospitalization, and indwelling devices (Minasyan 2017). Approximately one-third of sepsis cases occur in the postoperative period (Armstrong et al. 2017). Respiratory, gastrointestinal, genitourinary, and skin and soft tissue infections are the most common sources of sepsis. Pneumonia is the most common cause of sepsis (Gauer et al. 2020).

The standard treatments for sepsis include fluid resuscitation, antimicrobial therapy, vasopressor therapy, and other interventions (corticosteroids, blood products, glycemic control, nutrition, and source control) (Gauer et al. 2020). Source control in the management of sepsis includes rapid determination of the site of infection and identification of a focus of infection amenable to source control measures (specifically the drainage of an abscess, debridement of infected necrotic tissue, removal of a potentially infected device, and definitive control of a source of ongoing microbial contamination) (Dellinger et al. 2013).

Ta1 is not mentioned as an option for the treatment of any aspects of sepsis in the treatment guidelines of the American Academy of Family Physicians (Gauer et al. 2020), the Surviving Sepsis Campaign (SSC) International Guidelines for the Management of Sepsis and Septic Shock (Dellinger et al. 2013 and Evans et al. 2021), or the Policy Statement by the American College of Emergency Physicians (Yealy et al. 2021).

a. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

The nomination cited two references related to Ta1 in the treatment of sepsis. The first article (Yu et al. 2009) is a systematic review of the efficacy of Ta1 in the treatment of sepsis. The

review included five clinical trials and concluded that there is insufficient evidence of decreased mortality in sepsis. This article is available only in abstract form; the full text is in Chinese. The abstract did not provide sufficient details to assess and verify the results.

The article by Wang et al. (2016), is a systematic review and meta-analysis of the efficacy and immunomodulatory effect of ulinastatin and Ta1 for sepsis. The studies included in this meta-analysis compared the combination of ulinastatin with Ta1 to controls. Ulinastatin is not approved for any indication in the United States. Based on the context of the article, ulinastatin is presumably an anti-inflammatory agent that has been used clinically, including as a substitute for steroids. Because the article does not provide data on the efficacy of Ta1 alone in the treatment of sepsis, it cannot inform our evaluation of Ta1's effectiveness for this proposed use.

We identified several other articles on the use of Ta1 in sepsis. Most were in Chinese with abstracts in English. These articles did not provide sufficient details on methodology used in or results of any studies. In addition, some of the articles reported on studies in which Ta1 was used in combination with other drugs that are not approved for any indication in the United States, i.e., ulinastatin and Xuebijing. These studies were not reviewed because they did not provide efficacy information for Ta1 as monotherapy. Review or opinion articles were also excluded from our evaluation because they did not provide unique efficacy data. Only four full articles in English describing studies of Ta1's use in sepsis have been published. They are summarized and discussed below.

Wu et al. (2013) conducted a multicenter, single-blind, RCT evaluating the efficacy of Ta1 for severe sepsis (ETASS). A total of 361 patients with severe sepsis were randomized to the control (n=180) or Ta1 (n=181) group. Ta1 1.6 mg/mL (Zadaxin, SciClone Pharmaceuticals) or normal saline 1 mL was injected SC twice a day for five consecutive days, then once per day for two consecutive days. The primary endpoint was 28-day all-cause mortality. Secondary endpoints included dynamic changes of Sequential [Sepsis-related] Organ Failure Assessment (SOFA)[208], CD4+/CD8+, and monocyte human leucocyte antigen-DR (mHLA-DR) expression measured on day 0, 3, and 7. The mortality rate from any cause within 28 days in the Ta1 and control groups were 47/181 (26%) and 63/180 (35%), respectively with an absolute reduction in mortality of 9% (95% CI: -0.5 to18.5, p=0.062). In the time-to-event analysis, patients in the Ta1 group survived longer after enrollment than those in the control group (log rank, p=0.049). The relative risk of death in the Ta1 group as compared to the control group was 0.74 (95% CI 0.54 to 1.02). There was no significant difference in ICU mortality, length of ICU stay, and duration of ventilation between the two groups. The CD4/CD8 ratio did not change over 7 days in both groups. The mHLA-DR level increased in both groups, to a greater degree in the Ta1 group compared to the placebo group on day 3 (p=0.037) and day 7 (p=0.017). Prespecified analyses of the primary outcome, in which patients were stratified according to Acute Physiology and Chronic Health Evaluation II (APACHE II) score,[209] SOFA score, mHLA-DR level, and history of surgery or

[208] SOFA is a predictive tool that calculates the risk of death from sepsis. The SOFA score has three components, each of which are readily identifiable at the bedside and are allocated one point: respiratory rate ≥22/minute, altered mentation, systolic blood pressure ≤100 mmHg (Seymour et al. 2016). A SOFA score of 2 points or more is associated with an in-hospital mortality greater than 10%.

[209] The APACHEII score, introduced in 1985, is a modification of the original APACHE developed in 1981. It is a

cancer, showed that Ta1 tended to improve outcome but without statistical significance. The authors concluded that Ta1 "…may be effective in improving clinical outcomes in a targeted population of severe sepsis. Larger multicenter studies are indicated to confirm these results." The study had several limitations, including that the study was not double-blinded, and the biomarkers were tested only on day 3 and day 7. In addition, mHLA-DR levels were lower at baseline in the Ta1 group compared to placebo, which may have contributed to the greater improvement. The article did not report on the other treatments the patients received, i.e., surgical drainage or other source control efforts that may have contributed to the outcomes.

Pei et al. (2020) conducted a post-hoc analysis of the ETASS study by Wu et al. The objective was to assess early immune status in adult septic patients and its relevance to hospital mortality. Only patients with mHLA-DR measured within 48 hours after onset of sepsis were enrolled in the study (273 out of 361). In-hospital mortality was higher only in elderly patients (> 60 years) with mHLA-DR <30% (immunoparalysis) compared to the elderly patients with HLA-DR >30%. Analysis of patients with sepsis who did not receive Ta1 treatment yielded the same results, i.e., early immunoparalysis was independently associated with increased in-hospital mortality in elderly, but not in non-elderly, subjects. The authors did not provide results for the subpopulation of subjects who received Ta1 in the study.

Because the systemic inflammatory response seen in severe acute pancreatitis can overlap with the severe acute systemic inflammation seen in sepsis, we reviewed additional investigations that could potentially inform the review of Ta1 in sepsis. Wang et al. (2011) performed a prospective, R, DB pilot study to evaluate the effects of Ta1 on immunomodulation and clinical outcomes in patients with severe acute pancreatitis admitted to Jinling Hospital. A total of 24 patients were randomized to conventional therapy or Ta1 (SciClone Pharmaceuticals, USA)[210] 3.2 mg twice daily for 7 days. To assess immune function, HLA-DR expression was monitored before and after treatment. The authors state that increase in the HLA-DR level was greater at day 8 in the Ta1 group compared to the control group. There were no deaths reported in both groups. The following results were reported: the rate of positive blood and abdominal drainage cultures over the 28-days of follow-up period in Ta1 group was significantly lower than in the control group (p=0.027). The rate of surgery was 33% in Ta1 patients compared to 83% in the control group (p=0.036). The authors concluded that "a larger clinical trial should be conducted to validate the conclusions of the present study."

The study had several limitations. The sample size was small. Patients in the Ta1 group, although not statistically significant, were younger and had lower APACHEII scores, and therefore, possibly less severe disease. The study was conducted at a single hospital. The patient population with severe pancreatitis is representative of only a subset of patients with sepsis. The article had several discrepancies such as varying p-values in different sections for the same outcomes, i.e.,

scoring system aimed to determine the severity of disease and to predict mortality of adult patients admitted to intensive care units. (Knaus 1985). The APACHE-II scoring system has three domains: "Acute Physiology", "Chronic Health Evaluation" and "Age." The score of $\geq$ 25 was considered of high risk of death. This scoring system is no longer recommended for the assessment of sepsis.

[210] The specific formulation of Ta1 was not described, i.e., whether the product's concentration was 3.2 mg/mL or 1.6 mg/mL given as 2 mL. The ROA was also not specified; the study only stated that patients were injected.

the p-value for the rate of surgery was 0.036 and 0.069. Some results were reported only as p-values or percentages without numerical values.

Bai et al. (2022) conducted an RCT to explore the effects of Ta1 plus blood purification (BP) on septic shock patients. A total of 43 patients (intervention group) received Ta1 (SciClone Pharmaceuticals) 1.6 mg SC plus BP twice a week and 43 patients (control group) received BP (regimen not specified); both groups were treated continuously for 10 days. The article did not describe the blood purification therapies used.[211] In addition, the subjects received ulinastatin once every 12 hours (duration of treatment not specified). Treatment efficacy was evaluated at 10 days postintervention; if the subject had regained consciousness and was in a stable condition, the research team considered the treatment to be markedly effective. Authors state that the intervention group showed a significantly shorter duration of shock and length of stay in the ICU, a significantly higher overall response rate, and improvements in T-lymphocyte subsets, inflammatory cytokines, and myocardial function ($p<0.05$). Follow-up of 32 subjects in the intervention group and 35 in the control group at 12 months showed no significant difference in survival, with 11 deaths in the intervention group and 9 in the control group. The study had several limitations, including lack of blinding, small size, and vague definitions of efficacy criteria. In addition, the use of concurrent therapies hampers our ability to assess the contribution of Ta1 to effectiveness. Ulinastatin is not approved in the United States for any indication, and blood purification is not a standard therapy for sepsis under current treatment guidelines.

Clinicaltrials.gov lists four studies of Ta1 in sepsis, all conducted in China. The results of these studies are not available in clinicaltrials.gov, and we could not locate related publications.

b. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

Sepsis is a serious and life-threatening condition with a high mortality rate.

c. Therapies that have been used for the condition(s) under consideration

There are not FDA-approved drug products indicated for the same medical condition as FDA has evaluated for the proposed compounded drug product containing Ta1-related BDSs. However, there are FDA- approved drug products that have been used to treat certain aspects of sepsis including antibiotics; vasopressors such as norepinephrine; and IV crystalloid solutions.

d. Conclusion

We conclude that 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 a meaningful clinical benefit of Ta1 in the treatment of sepsis, e.g., reduction in mortality or need for organ support. Design of the studies, such as lack of double blinding, small samples, short follow-up, and/or use of other

[211] Blood purification is proposed as an adjuvant therapy for sepsis, aiming at controlling the associated dysregulation of the immune system. Depending on the membrane, the blood purification devices are used for removal of cytokines, endotoxins, or pathogens; replacement of renal function, or to offer antithrombogenic treatment. (Monard et al. 2019)

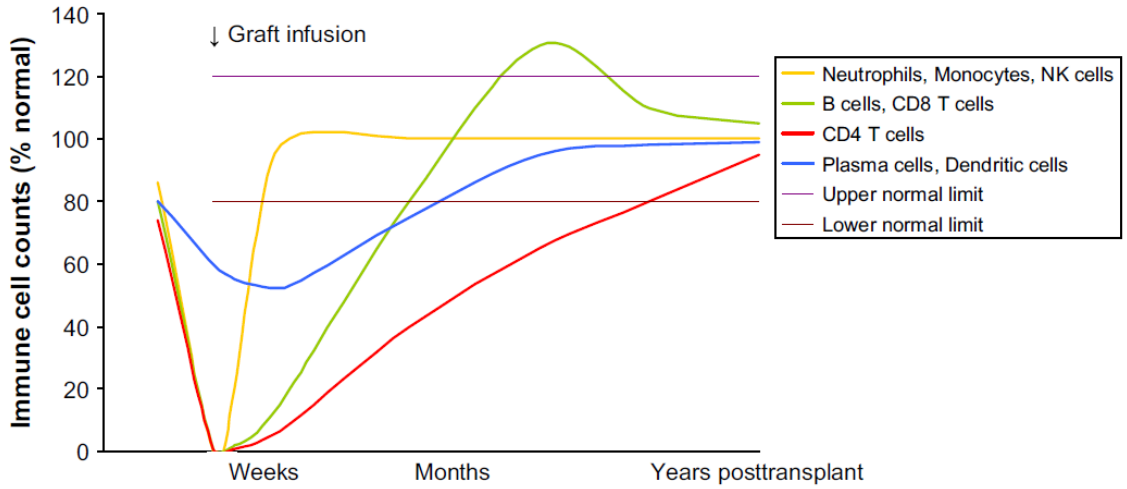
concomitant therapies, limit our ability to assess the contribution of Ta1 to efficacy. It is important to note that all of the available clinical studies were conducted outside the U.S., exclusively in China, where the patient population may not be reflective of the U.S. population. Based on the studies reviewed in this section, treatment of sepsis in China may not be reflective of the U.S. medical practice. Professional treatment guidelines do not mention Ta1 as an option in the management of sepsis.

10. Infections after hematopoietic stem cell transplantation (HSCT)

Hematopoietic stem cell transplantation (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) (Tomblyn et al. 2009). The goal of HSCT is lifelong engraftment of the administered cells, resulting in some or all of the recipient's lymphohematopoietic system being derived from the HSC graft (Tomblyn et al. 2009). HSCT is used as a treatment in a variety of benign and malignant diseases. While allogeneic HSCT may be used for the treatment of diseases such as leukemia, myeloproliferative disorders, myelodysplastic syndrome, and congenital immunodeficiencies; autologous HSCT may be used for hematologic recovery following high dose chemotherapy in patients with diseases such as multiple myeloma, lymphoma, and neuroblastoma.

Immune reconstitution describes a process of rebuilding the immune system after HSCT. Briefly, neutrophil, monocyte, and natural killer cell recovery is followed by platelet and red cell recovery, which is followed by B and T cell recovery (Tomblyn et al. 2009) (Figure 13). In contrast to relatively early recovery of innate immune cells, recipients of HSCT experience prolonged deficiencies in T cells and B cells, which can take up to two years to fully recover.

Figure 13. Approximate Immune Cell Counts (Expressed as Percentage of Normal Counts) Pre- and Post Myeloablative Conditioning (Tomblyn et al. 2009).

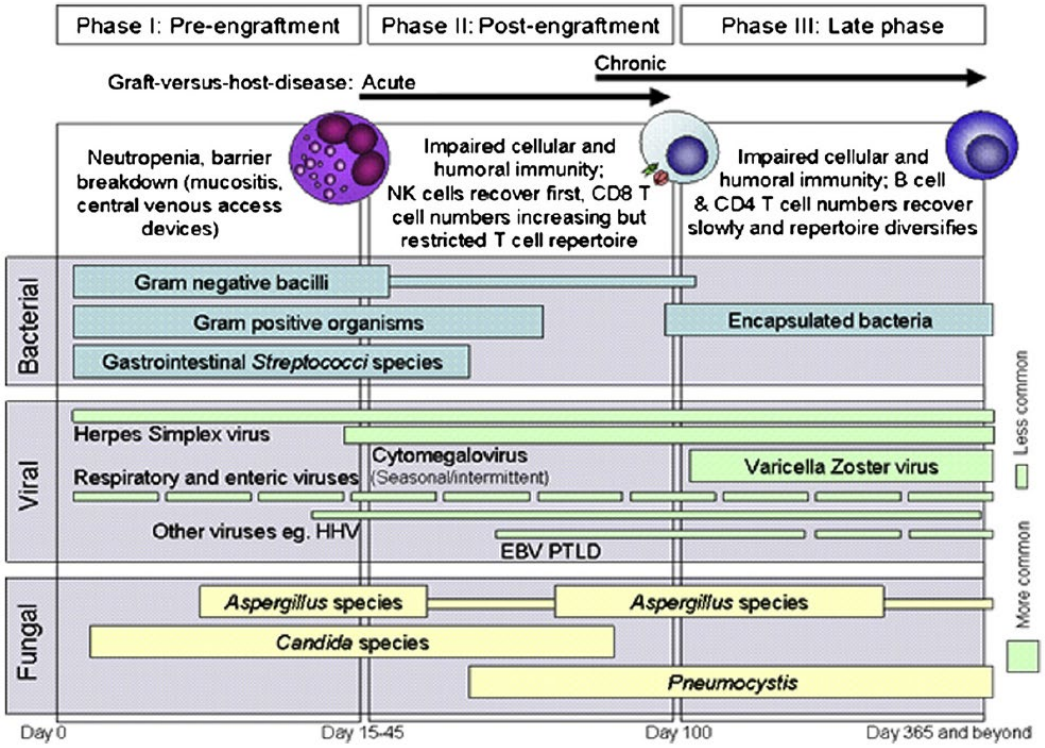


The major causes of early morbidity and mortality for patients who undergo HSCT are disease relapse, acute graft-vs-host disease (aGVHD),[212] infection, regimen related toxicity, and graft failure (Tomblyn et al. 2009). The risk of infection after HSCT is primarily determined by the time from transplant and the presence or absence of GVHD. Other factors that influence the risk of infection include donor/host histocompatibility, disease status, graft type, graft contents/dose, conditioning intensity, and neutrophil engraftment.

There are generally three phases of potential infectious complications after HSCT (Tomblyn et al. 2009). Phase I, or the pre-engraftment phase (<15-45 days after HSCT), is characterized by prolonged neutropenia and breaks in the mucocutaneous barrier, which result in a substantial risk of bacteremia and fungal infections involving *Candida* species, and as neutropenia continues, *Aspergillus* species. In addition, herpes simplex virus (HSV) reactivation may occur during this time. Phase II, or the post-engraftment phase (30-100 days post HSCT), is characterized by impaired cell-mediated immunity and is directly related to the severity of GVHD and immunosuppressive therapy. Herpesvirus, cytomegalovirus (CMV), *Pneumocystis jiroveci*, and *Aspergillus* species are common pathogens during this phase. During phase III, or the late phase (more than 100 days post HSCT), the risk of infection corresponds to the severity of the patient's GVHD during the first two phases. Common pathogens include CMV, varicella-zoster virus, and infections from encapsulated bacteria, such as *Streptococcus pneumoniae*. See Figure 14.

[212] Graft-versus-host disease is a condition that occurs when donated stem cells or bone marrow (the graft) see the healthy tissues in the patient's body (the host) as foreign and attack them. Graft-versus-host disease can cause damage to the host's tissues and organs, especially the skin, liver, intestines, eyes, mouth, hair, nails, joints, muscles, lungs, kidneys, and genitals. The signs and symptoms may be severe and life threatening. Graft-versus-host disease can occur within the first few months after transplant (acute) or much later (chronic). Also called GVHD. See https://www.cancer.gov/publications/dictionaries/cancer-terms/def/graft-versus-host-disease. Accessed June 5, 2024.

Figure 14. Phases of Opportunistic Infection Among Allogenic HCT Recipients (Tomblyn et al. 2009)



EBV- Epstein-Barr virus; HHV6- human herpesvirus 6; PTLD- posttransplant lymphoproliferative disease

Various strategies are employed pre and/or post HSCT to prevent or treat infections during the period of altered immunocompetence after HSCT. These include close monitoring, use of growth factors (granulocyte colony-stimulating factor), prophylactic antimicrobials, and pre-emptive treatment at the earliest sign of infection. Such infections are addressed by antimicrobial agents including antibiotics (e.g., levofloxacin), antivirals (e.g., acyclovir or valacyclovir, letermovir), antifungals (e.g. posaconazole, voriconazole, and isavuconazole), and anti-*Pneumocystis*/anti-toxoplasmosis agents (e.g., trimethoprim/sulfamethoxazole). Culture results and PCR test results are used to guide treatment.[213]

In the United States, guidelines for the prevention of infectious complications among HSCT recipients are available from the American Society of Transplantation and Cellular Therapy (ASTCT), which was formerly known as the American Society for Bone and Marrow Transplantation (ASBMT) (Tomblyn et al. 2009). In addition, ASCO and IDSA have guidelines on antimicrobial prophylaxis for adult patients with immunosuppression associated with cancer and its treatment (Taplitz et al. 2018). It should be noted that the ASTCT, ASBMT and ASCO/IDSA guidelines do not mention Ta1 in their recommendations.

[213] American Society of Transplantation and Cellular Therapy Guidelines for Infection Prophylaxis, Monitoring, and Therapy in Cord Blood Transplantation, https://www.astctjournal.org/article/S2666-6367(21)00633-3/fulltext.

Considerations for Assessing Effectiveness

In HSCT trials, the regulatory decision may be based on endpoints that can translate to meaningful clinical benefit, in addition to survival endpoints. Omisirge is an example of a product that has recently been approved by FDA based on demonstration of a clinical benefit in patients receiving HSCT by reducing the time to neutrophil recovery and reducing the incidence of infection.[214]

a. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

We identified two published studies using Ta1 in subjects who received HSCT. These studies are described in Appendix 3 and are organized chronologically. Ta1 was administered as a daily 1.6 mg SC injection for 16 weeks (Perruccio et al. 2010) or as a 1.6 mg SC injection twice a week for 4 weeks (Ding et al. 2013). A variety of immune markers were measured in the studies.

Perruccio et al. (2010) described a single arm study in 8 sibling HLA matched and 6 haploidentical HSCT recipients who received Ta1 after transplantation. Authors concluded that Ta1 is safe and may favorably affect immune function. However, they note that a larger number of subjects and longer follow-up are needed to assess its impact on survival. It is unclear from the article when the subjects initiated Ta1.

From the literature, it appears that authors published several meeting abstracts reporting subsequent results on the same or a similar set of subjects (Perruccio et al. 2011; Ruggeri et al. 2012). For example, Perruccio et al. (2011) describes a study in 30 recipients (12/30 with active disease at transplant) of HLA (human leukocyte antigen)-matched sibling T cell-depleted stem cell transplant recipients who received 1.6 mg Ta1 SC daily from the day of transplantation for 16 weeks. Forty-five subjects (25/45 with active disease at transplant) who were transplanted under the same protocol served as controls. Here, authors reported that the cumulative incidence of non-relapse mortality (mainly infection related) was 33% in controls vs 7% in Ta1 treated subjects. Per authors, Ta1 administration did not impact the relapse rate (~50% in both series) and Ta1 was identified as an independent factor predicting a lower incidence of non-relapse mortality in a multivariate analysis. The authors concluded that Ta1 could be safely administered after matched sibling T cell depleted HSCT and that it protected against largely infectious non-relapse mortality and improved the survival of transplant recipients. Although Perruccio et al. (2011) reported a potential improvement in non-relapse mortality, the details needed to assess the impact of Ta1 are lacking because it was a meeting abstract. For example, it is unclear if there was a concurrent control group, there was no information on the primary endpoint, the follow-up duration is unclear, and there are no details on infectious complications post-HSCT.

Ding et al. (2013) described a case series of eight subjects, four of which received Ta1 (treatment group) and four did not (control group) following HSCT. The authors concluded that Ta1 might

[214] See label for Omisirge (omidubicel-onlv), BLA 125738, accessed 9/26/24, https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=979803c9-956c-42e7-9d75-c37cc4e90632.

affect cytokine levels and immune cells. However, the infection rate did not decrease. The timing of Ta1 initiation after HSCT and the follow-up duration are unclear. Table 11 shows the baseline characteristics of the eight subjects included in the study.

Table 11. Baseline Characteristics (Adapted from Ding et al. 2013).

	Treatment group	Control group
	Ta1 (n=4)	No Ta1 (n=4)
Baseline characteristics	N (%)	N (%)
Allo HSCT	3 (75)	4 (100)
Auto HSCT	1 (25)	0 (0)
Active disease	0 (0)	3 (75)
Complete remission	3 (75)	0 (0)
Infections		
Fungal infections	4 (100)	1 (25)
Viral infections		
CMV infection	2 (50)	1 (25)
HBV	0 (0)	1 (25)
Tuberculosis	0 (0)	1 (25)
Unknown infections	0 (0)	1 (25)

We have concerns about subject selection. The case series included a control group comprising four high-risk subjects, three of whom had active disease prior to HSCT. Three of the four subjects in the Ta1 treatment group were in complete remission prior to transplant, and therefore are considered much lower risk. Despite this imbalance, which was in favor of the Ta1 group, the subjects who received Ta1 developed more infections. For example, (i) all subjects in the Ta1 treatment group developed fungal infections (100%) compared to one subject (25%) in the control group and (ii) there were 2 cases of viral infection in each group. Despite the small sample size, this raises a concern about whether treatment with Ta1 leads to an increased incidence of infections. The claim that Ta1 reduces the infection rate is not in alignment with the data from this case series. Additionally, it is challenging to conclude that the markers measured correlate with a reduction in infection rates after HSCT.

In summary, these studies do not provide evidence that Ta1 is effective at reducing infections after HSCT. The results of these publications are challenging to interpret due to heterogeneous subject populations, small sample size, limited duration of follow up, lack of clinically meaningful endpoints, unclear clinical relevance of the measured markers, and missing details relevant to outcomes. Furthermore, the authors have not reported important details about the study design that could affect the outcome of HSCT, such as the preconditioning regimen, GVHD prophylaxis, graft source, degree of match between donor and recipient, underlying disease, age of the subject, concomitant medications, and the duration of follow up.

It is also important to note that the available publications are over a decade old, and there are several additional limitations to their interpretability including but not limited to: there was no

information on further studies to confirm benefit; none of the reported cells (dendritic cells/ CD8+ T cells/ T regs) have been approved for any disease indication in the United States; none of the reported cells (dendritic cells/ CD8+ T cells/ T regs) are used as standard markers in clinical practice in the United States; the authors did not provide information on the validity of the assays used to measure cell counts/function or any of the immune markers; and none of the in vitro tests of the reported cells were shown to correlate with a decrease in the infection rate.

b. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

Infections after HSCT can be serious and life-threatening.

c. Therapies that have been used for the condition(s) under consideration

There are FDA-approved drug products that treat the same medical condition as FDA has evaluated for the proposed compounded drug product containing Ta1-related BDSs.

There are FDA-approved drug products for preventing or treating infections, some of which are specifically indicated after HSCT. For example:

- Letermovir (Prevymis); indicated for prophylaxis of cytomegalovirus (CMV) infection and disease in adult and pediatric patients 6 months of age and older and weighing at least 6 kg who are CMV-seropositive recipients [R+] of an allogeneic HSCT.
- Micafungin sodium (Mycamine); indicated in adult and pediatric patients for prophylaxis of *Candida* infections in adult and pediatric patients 4 months of age and older undergoing HSCT.
- Ganciclovir; indicated for the prevention of CMV disease in adult transplant recipients at risk for CMV disease.
- Posaconaxole; indicated for the prophylaxis of invasive *Aspergillus* and *Candida* infections in patients who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy.
- Maribavir; indicated for the treatment of adults and pediatric patients (12 years of age and older and weighing at least 35 kg) with post-transplant cytomegalovirus (CMV) infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir or foscarnet.
- Cefepime; indicated for empiric treatment of febrile neutropenic patients. In patients at high risk for severe infection (including patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying hematologic malignancy, or with severe or prolonged neutropenia).

In addition, there are several FDA-approved drug products used for preventing or treating infections that are not specifically indicated after HSCT as described in the ASTCT (Tomblyn et al. 2009) and the ASCO/IDSA (Taplitz et al. 2018) guidelines.

d. Conclusion

In summary, these studies do not provide evidence that Ta1 is effective at reducing infections and/or infection related mortality after HSCT. The limitations of the published studies include their small size, heterogeneity in study design and population, unclear clinical relevance of the measured markers, no information on the assays used to measure the markers, and limited details of the study populations, treatments, and outcome measures. Given these limitations, no conclusion can be drawn regarding the effectiveness of Ta1 in reduction of infection following HSCT.

11. Chronic obstructive pulmonary disease (COPD)

COPD is a lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production and/or exacerbations) due to abnormalities in the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that causes persistent, often progressive, airflow obstruction and is not fully reversible. The diagnosis of COPD is confirmed by the presence of non-fully reversable airflow obstruction (i.e., forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) (FEV1/FVC) < 0.7 post-bronchodilation) measured by spirometry. In most patients, COPD is associated with significant concomitant chronic diseases, which increase morbidity and mortality.

The goals of treatment for COPD are to control symptoms, improve quality of life and reduce exacerbations and mortality. Non-pharmacological approaches to treatment include smoking cessation, nutritional support, pulmonary rehabilitation, and oxygen therapy for those with resting hypoxemia. Pharmacotherapy can reduce COPD symptoms, reduce the frequency and severity of exacerbation, and can improve health status and exercise tolerance. Treatment regimens should be individualized and guided by factors including severity of symptoms, risk of exacerbations, side-effects, co-morbidities, and patient response. Pharmacotherapy is generally initiated in a stepwise fashion, depending upon assessment of the level of symptoms and risk of exacerbations. The commonly used drug classes for COPD include bronchodilators such as beta2-agonists (short acting beta2-agonists (SABA) and long acting beta2-agonists (LABA)), antimuscarinics (short-acting antimuscarinic agents (SAMA) and long-acting antimuscarinics (LAMA)); inhaled corticosteroids (ICS) or systemic glucocorticoids; phosphodiesterase-4 (PDE4) inhibitors, and antibiotics. Acute exacerbations of COPD can be managed in an outpatient or inpatient setting depending on the severity (Agarwal et al. 2023).

Ta1 is not mentioned for COPD treatment in the guidelines of professional societies such as Pharmacologic Management of COPD: An Official American Thoracic Society (ATS) Clinical Practice Guideline (Nici et al. 2020), the Global Initiative for Chronic Obstructive Lung Disease (Agusti et al. 2023), and the Pharmacologic Management of COPD Exacerbations: A Clinical Practice Guideline from the American Academy of Family Physicians (AAFP) (Stevermer et al. 2014).

a. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

Our search of published medical literature retrieved two references in English that include information on the effectiveness of Ta1 for COPD.

Jia et al. (2015) explored the efficacy of Ta1 plus "routine complex treatment" in 84 patients with a history of acute exacerbation of COPD in a R, DB trial. The authors hypothesized that Ta1 possibly modulates immune imbalance in patients with COPD through a "certain kind" of mechanism and thus enhances their immune function. Included were patients with COPD with FEV1 <80% of predicted value and symptoms in the acute aggravation stage, which included at least one of the following: worsening of cough, increase of sputum quantity and purulent sputum, and worsening of dyspnea, fever, and complicating pneumonia. All patients received "routine complex treatment" (not specified in the article) including anti-infective, anti-inflammatory, spasmolytic. Patients in the experimental group additionally received SC injections of Ta1 1.6 mg once daily for 5 days then once every two days from day 6 until week 4, while the control group received placebo (42 per group).

To evaluate efficacy, the following were measured before and after treatment: FEV1 and FVC, pressures of oxygen (PaO_2) and pressure of carbon dioxide ($PaCO_2$), general health status (assessed by the Short-Form 36-Item Health Survey)[215] and serum cytokine levels (plasma T cell subsets and IFN- γ, IL-4, IL-8, and leukotrienes B4). The authors stated that PaO2, PaCO2, FEV1 and FEV1/FVC improved in both groups, and that the experimental group showed "more pronounced" improvement compared to the control group and claimed SF-36 survey scores showed that only the experimental group "improved significantly." The authors added that the CD4+ T lymphocyte count, serum IFN-g levels, and the ratios of CD4+/CD8+ and IFN-γ/IL-4 of both groups "significantly increased" after treatment, while the CD8+ T lymphocyte count and levels of IL-4, IL-8, and LTB4 of both groups significantly decreased after treatment with "more pronounced improvement" in the experimental group. The authors claim these results indicate that "Ta1 could enhance the activity of helper T cells, thus improving cellular immune function" and concluded "routine treatment plus Ta1 could improve the immune function of acute exacerbation COPD patients and efficiently inhibit inflammatory reaction."

Limitations of this study include the following: (1) there is inadequate information on clinically relevant outcome measures in the context of patients hospitalized for acute exacerbations of COPD; (2) small sample size; (3) short duration; (4) there is limited information provided on concomitant or background COPD medications ("routine complex treatment"); (5) conducted entirely in China, such that the generalizability of the study to the US population is uncertain.

Liu et al. (2023) investigated the effect of combined administration of theophylline sustained-release tablets (theophylline SR) and Ta1 on pulmonary function, immunity, and inflammation. The study included 122 elderly patients 67 to 74 y/o who suffered from an acute attack of COPD with respiratory failure. After admission, patients in the two groups were treated with expectorants, antispasmodics, glucocorticoids, and anti-infectives; all the patients received non-invasive positive pressure ventilation. The control group received oral 0.2 g theophylline SR

[215] The Short-Form 36-Item Health Survey (SF-36) has eight subscales and two component scores: physical component summary (PCS) and mental component summary (MCS). Higher SF-36 score indicated better quality of life for the patients. For more information see RAND Medical Outcome Study, accessed 6/11/24 https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form.html

twice a day, while the treatment group received oral 0.2 g theophylline SR twice a day and IV injection 1.6 mg Ta1 twice a week for 4 weeks (61 per group). The parameters measured before and after treatment included pulmonary function indicators (FEV1/FVC), blood gas indicators (PaCO2, PaO2, blood oxygen saturation (SaO2)), inflammatory markers (sICAM-1, PGE2, hs-CRP, T helper cells, regulatory T cells), and exercise ability (6-minute walking distance). The authors stated, "in this study, pulmonary function and blood gas indicators, levels of inflammatory factors and immune cells, and exercise ability of patients in the two groups did not differ before treatment, and they all improved after treatment in both groups with better effects observed in the study group than in the control group." The authors claim that "[Ta1] improves and optimizes patient immunity and ameliorates the inflammatory response by regulating immune function." They also acknowledge that further clinical trials are required prior to application of this combination therapy in clinical practice.

We note limitations of this study include the small sample size, short duration, lack of meaningful clinical endpoints for the inpatient COPD exacerbation population, and lack of details on concomitant medications used by COPD patients. In addition, the patient population was only elderly adults; hence, the applicability of the results to other populations is unclear.

A search of clinicaltrials.gov did not retrieve any studies on the use of Ta1 for COPD.

b. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

COPD can be serious or life-threatening.

c. Therapies that have been used for the condition(s) under consideration

There are FDA-approved drug products that treat the same medical condition as FDA has evaluated for the proposed compounded drug product containing Ta1-related BDSs. The following list includes currently available FDA-approved drug products indicated for COPD separated by class with an example for each:

- Short-acting bronchodilators; albuterol sulfate
- Long-acting bronchodilators; salmeterol
- Inhaled steroids; fluticasone
- Combination bronchodilators and inhaled steroids; salmeterol/fluticasone
- PDE4 inhibitors; roflumilast
- Methylxanthines; theophylline

d. Conclusion

Based on available data, there is a lack of evidence to support the effectiveness of Ta1 for the treatment of COPD, which can be a serious or life-threatening disease. While authors claim that studies suggest that there are "better effects" observed in the those who received Ta1 compared to the control group, the available information is limited to small studies of short duration that lack sufficient details about statistical methodology and other important study design elements

e.g., blinding. Further, the lack of sufficient information on concomitant medications taken by the patients limits interpretation of study results and raises concerns regarding the generalizability of the results to a U.S. population. Lastly, for one of the studies (Lie et al. 2023), there were no clinically meaningful endpoints evaluated relative to the study population enrolled (inpatients with COPD exacerbation population). In addition, there are multiple, currently available FDA-approved drug products indicated for the treatment of COPD.

12. Myalgic encephalomyelitis and chronic fatigue syndrome (ME/CFS)

ME/CFS is a complex, chronic, debilitating disease. According to the CDC, the core symptoms needed for diagnosis include: 1. The reduced ability to perform pre-illness activities that lasts for more than 6 months. This reduced ability is accompanied by profound fatigue not improved by rest. 2. Post-exertional malaise (PEM). PEM is a hallmark of ME/CFS with symptoms that worsen after physical, mental, or emotional effort. 3. Unrefreshing sleep. In addition, patients must also have orthostatic intolerance and/or cognitive impairment. The exact cause or causes of ME/CFS are unknown. However, up to 80% of patients develop ME/CFS following an acute viral-like illness. In most cases, the cause of the infection is unknown. Patients have reported ME/CFS-like illness following COVID-19, otherwise known as long COVID.[216]

There are no FDA-approved drug products indicated for the treatment of ME/CFS. Treatment of ME/CFS is aimed at supportive and symptomatic care (non-pharmacologic and pharmacologic) based on the subject's specific disease manifestations/symptoms.

a. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

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

b. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

ME/CFS is a serious condition.

c. Therapies that have been used for the condition(s) under consideration

There are no FDA-approved drug products that treat the same medical condition as FDA has evaluated for the proposed compounded drug product containing Ta1-related BDSs.

d. Conclusion

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

Overall Conclusion of Effectiveness: Based on available data, we conclude that there is a lack of evidence to support the effectiveness of SC Ta1 (free base) and Ta1 acetate for use in hepatitis B, hepatitis C, HIV, COVID-19, depressed response to vaccinations; adjuvant to flu vaccines,

[216] See CDC website at https://www.cdc.gov/me-cfs/hcp/clinical-overview/index.html and https://www.cdc.gov/me-cfs/causes/index.html. Accessed June 11, 2024.

malignant melanoma, HCC, NSCLC, sepsis, infections after HSCT, COPD, and ME/CFS. For evaluated uses that have clinical practice guidelines for U.S. health professionals, the guidelines do not mention 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 (e.g., retrospective or single arm studies; lack of a control group or use of outdated therapy in the control arm, including the use of unapproved products or outdated treatment(s) regimens and non-preferred concomitant therapies; lack of randomization and/or blinding; choices of efficacy endpoints that were of unclear clinical relevance; heterogeneity in study populations and between studies in definitions of disease severity). Additionally, there is no evidence to suggest that Ta1 monotherapy, or Ta1 with other therapies would provide an advantage over standard of care alone. Because patients in the underlying studies for some of the evaluated uses did not receive the current U.S. standard of care, it is unknown whether Ta1 would provide clinical benefit for those uses in current settings.

There are multiple FDA-approved drug products indicated for use in the treatment of many of the conditions evaluated.

III. CONCLUSION AND RECOMMENDATION

We have balanced the criteria described in section II above to evaluate Ta1-related bulk drug substances for the 503A Bulks List. After considering the information currently available, a balancing of the criteria ***weighs against*** both Ta1 (free base) and Ta1 acetate being placed on that list based on the following:

1. Conclusions on the physical and chemical characterization for each Ta1-related BDS, Ta1 (free base) and Ta1 acetate, are included in subsections 1.1 and 1.2., respectively.

    1.1. Ta1 (free base) is a peptide of 28 amino acids. As reported in the literature, Ta1 (free base) is expected to be stable under storage conditions below -18°C. However, the stability of peptides, such as Ta1 (free base), is highly sensitive to the manufacturing process and quality attributes of the compounded or finished drug product.

    Ta1 (free base) is not well-characterized from the physical and chemical characterization perspective because certain critical characterization data specific to Ta1 (free base), including impurities, aggregates, bioburden, and bacterial endotoxins, were not found in publicly available scientific literature and the nomination package lacked information to establish identity, purity, and impurity profiles of the substance, such as specific tests in COAs. As discussed in Section II.C.2.d., FDA is concerned about the potential for immunogenicity of Ta1 (free base) when formulated in an injectable dosage form for SC administration due to the potential for aggregation as well as potential peptide-related impurities, as discussed in Section II.A.1.c. Injectable routes of administration may present a particular risk for immunogenicity.

    In addition, due to limited water solubility of Ta1 (free base), it is unclear how it would be possible to formulate the proposed injectable dosage form with a concentration of 3 mg/mL, and no information was provided to explain how this solubility could be achieved.

    1.2. Ta1 acetate is an acetate salt of the Ta1 (free base) peptide of 28 amino acids. As reported in the literature, Ta1 acetate is expected to be stable under storage conditions below 20°C. However, the stability of peptides, such as Ta1 acetate, is highly sensitive to the manufacturing process and quality attributes of the compounded or finished drug product.

    Ta1 acetate is not well-characterized from the physical and chemical characterization perspective because certain critical characterization data specific to Ta1 acetate, including impurities, aggregates, bioburden, and bacterial endotoxins, were not found in publicly available scientific literature and the nomination package lacked information to establish identity, purity, and impurity profiles of the substance, such as specific tests in COAs. As discussed in Section II.C.2.d., FDA is concerned about the potential for immunogenicity of Ta1 acetate

when formulated in an injectable dosage form for SC administration due to the potential for aggregation as well as potential peptide-related impurities, as discussed in Section II.A.1.c. Injectable routes of administration may present a particular risk for immunogenicity.

In addition, due to limited water solubility of Ta1 acetate, it is unclear how it would be possible to formulate the proposed injectable dosage form with a concentration of 3 mg/mL, and no information was provided to explain how this solubility could be achieved.

2. Ta1 was discovered in 1977. Published literature did not reveal studies in which compounded drug products containing Ta1 or Ta1 acetate were used in humans. OFs have not reported preparing compounded drug products containing Ta1 or Ta1 acetate. Internet search results for compounded drug products containing Ta1 indicate that Ta1 is being compounded as an injection and as a nasal spray. Compounded Ta1 is marketed for use in conditions such as Hepatitis B, Hepatitis C, HIV, chronic fatigue, inflammation, sepsis, COVID-19, Lyme Disease, allergies, cancer, asthma, COPD, and psoriatic arthritis. Ta1 is licensed and marketed in several countries. Ta1 is not recognized in the European or Japanese Pharmacopoeias.

3. From the nonclinical pharmacological perspective, Ta1 – the active moiety of Ta1 (free base) and Ta1 acetate – has immunomodulatory properties attributable to Ta1-induced activation of TLRs on dendritic cells and lymphoid progenitor cells. The immunomodulatory properties of Ta1 are thought to contribute to its ability to suppress cancer growth, sepsis, and viral infections in nonclinical in-vivo and in-vitro models. However, it is difficult to define the clinical relevance of the nonclinical pharmacological findings in part because: (i) the doses and ROAs of Ta1 are inconsistent across the studies, and (ii) most studies used fixed Ta1 doses that, according to BSA, translate to human equivalent doses markedly higher than the SC doses of Ta1 commonly used in clinical studies. In addition, concentrations of Ta1 shown to induce CD8+ T cells to release soluble factors that blocked HIV infection of macrophages and PBMCs in vitro were 2,000 times higher than the maximal plasma concentrations generated by the Ta1 dose commonly used in clinical studies. From the nonclinical toxicological perspective, summaries of nonclinical toxicity studies available in a product monograph from SciClone Pharmaceuticals, the maker of the internationally marketed drug product Zadaxin that contains Ta1 (free base, 1.6 mg/mL), suggest that Ta1 (free base) did not induce safety signals in acute and repeat-dose toxicity studies and in genotoxicity studies. However, the nonclinical data from these studies are not included in the monograph. In addition, the nomination did not include, and, at the time of this evaluation, FDA has not identified published nonclinical toxicity studies of Ta1(free base) or Ta1 acetate. Therefore, available nonclinical data are too limited to inform safety considerations for potential clinical uses of Ta1 (free base) and Ta1 acetate.

   Based on the available information for Ta1 (free base) and Ta1 acetate, we conclude that the use of Ta1-related BDSs in compounding may raise safety concerns.

In most clinical studies, Ta1 has been found to be well-tolerated and not associated with significant AEs attributable to Ta1 when administered in doses in the range of 1-16 mg via the SC ROA for up to 12 months. The most common dose in clinical studies was 1.6 mg via SC administration. The most common adverse reactions reported are local irritation, redness, or discomfort at the injection site. Information in the labels of Ta1 products marketed outside the United States includes warnings and contraindications when used in children, pregnant and lactating women, subjects with autoimmune diseases, and immunosuppressed populations. The Ta1 product label for Zadaxin in Indonesia includes information on transient increases in liver enzymes (characterized as flares) and recommendations about continuing Ta1 administration.

Although Ta1 has been found to be well-tolerated and not associated with significant AEs attributable to Ta1 in the literature, there may be concerns about its clinical use in compounding. For example, it is not clear whether the administration of Ta1 in patients undergoing HSCT could lead to the development or worsen acute GVHD or chronic GVHD and/or lead to engraftment failure. In addition, based on the data considered, safety data are insufficient to evaluate the risks associated with the use of Ta1 as a vaccine adjuvant with influenza vaccines licensed for use in the United States without an adequate assessment of risks, considering that the nominator of Ta1 is proposing for use in individuals with a depressed response, such as in the elderly, and as well as the lack of assessment of the optimal Ta1 dose and regimen.

The safety profile of compounded drug products containing Ta1 can be negatively impacted by various factors, including but are not limited to, the product formulation, peptide concentration, and storage conditions favoring the generation of product-related impurities and/or peptide aggregates capable of inducing untoward immunogenic responses. 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 and 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.

In addition, we are unaware of data to support the proposed 3 mg/mL strength Ta1 drug product. The highest strength of Ta1 administered in clinical trials to date is 2 mg/mL, and it is possible that a more concentrated solution could lead to aggregation and therefore increased immunogenicity potential. At the time of this evaluation, there are several currently available FDA-approved drug products indicated to treat many of the medical conditions reviewed in this evaluation.

4. Based on available data, we conclude that there is a lack of evidence to support the effectiveness of SC Ta1 (free base) and Ta1 acetate for use in hepatitis B, hepatitis C, HIV, COVID-19, depressed response to vaccinations; adjuvant to flu vaccines, malignant melanoma, HCC, NSCLC, sepsis, infections after HSCT, COPD, and ME/CFS. For evaluated uses that have clinical practice guidelines for U.S. health professionals, the guidelines do not mention 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 (e.g., retrospective or single arm studies; lack of a control group or use of outdated therapy in the control arm, including the use of unapproved products or outdated treatment(s) regimens and non-preferred concomitant therapies; lack of randomization and/or blinding; choices of efficacy endpoints that were of unclear clinical relevance; heterogeneity in study populations and between studies in definitions of disease severity). Additionally, there is no evidence to suggest that Ta1 monotherapy, or Ta1 with other therapies would provide an advantage over standard of care alone. Because patients in the underlying studies for some of the evaluated uses did not receive the current U.S. standard of care, it is unknown whether Ta1 would provide clinical benefit for those uses in current settings.

There are multiple FDA-approved drug products indicated for use in the treatment of many of the conditions evaluated.

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 is based on the lack of data related to physicochemical characterization, the insufficient safety information on the use of the substances, and the lack of evidence of effectiveness of the substances for use in hepatitis B, hepatitis C, HIV, COVID-19, depressed response to vaccinations; adjuvant to flu vaccine, malignant melanoma, HCC, NSCLC, sepsis, infections after HSCT, COPD, and ME/CFS. These substances are not well characterized from a physical and chemical characterization perspective. In addition, based on their limited solubility in water, it is unclear how it would be possible to formulate the proposed injectable dosage form as an aqueous solution with concentration of 3 mg/mL. FDA also did not identify information that addresses additional concerns related to potential aggregation and immunogenicity risks for Ta1 (free base) and Ta1 acetate, as described above. We have insufficient evidence of effectiveness to support the use of Ta1 (free base) or Ta1 acetate in the conditions evaluated. Our ability to interpret the clinical studies that are available is limited by factors including small sample sizes, trial design deficiencies, and the studies' use of outdated comparator therapies. The lack of evidence of effectiveness discussed above 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, weighs against Ta1-related BDSs being added to the 503A Bulks List. Accordingly, we propose not adding Ta1 (free base) or Ta1 acetate to the 503A Bulks List.

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V. APPENDIXES

APPENDIX 1: MELANOMA STUDIES

Author	Design	Population	Treatment	Objective	Results	Author Conclusion
Lopez et al. 1994	Single arm phase 2 study; Italy	46 subjects with metastatic melanoma (stage III and IV)	DTIC 850 mg IV on D1, Ta1 (Sclavo, Siena, Italy) 2 mg SC on D4-7, and IL-2 18 MU/m^2/d by continuous IV infusion on D8-12; cycles repeated q3w; max 6 cycles	Evaluate the effectiveness and toxicity of DTIC combined with Ta1 and continuous IV infusion of IL-2; chose Ta1 because of its reported immunomodulatory actions along with the absence of toxicity	Objective responses in 15 (36%) of 42 evaluable subjects; median time to progression 5.5 months; mean survival of 11 months	Combination of DTIC + Ta1 + IL-2 is active in the treatment of advanced melanoma with acceptable toxicity. "…present study did not allow us to assess the individual contribution of the agents used…"
Rasi et al. 2000	Phase 2 OL single arm study; Italy	26 subjects with unresectable metastatic melanoma (stage III and IV)	DTIC 200 mg/m^2 IV on D1-4, Ta1 (Sclavo, Siena, Italy) 1 mg SC on D8-11 and 15-18, and IFN-alpha 3 MU IM on D11 and 18; repeated q4w; max 9 cycles	Evaluate the safety and feasibility of triple therapy with Ta1 plus low dose IFN and DTIC in advanced metastatic melanoma pts	After a mean of 5.3 cycles, 10/20 (50%) of subjects responded (CR 25%; PR 25%); median time to progression 5.5 months; median survival time was 11.5 months	Results of this study indicate that the combination of DTIC, Ta1, and IFN is safe and well tolerated; overall response rate of 50% is encouraging.
Maio et al. 2010	Multicenter, OL, R study; 8 European countries	488 subjects with stage IV melanoma with unresectable metastases	Randomized to one of five treatment groups: DTIC + IFN-alpha + Ta1 (1.6 mg SC); DTIC + IFN-alpha + Ta1 (3.2 mg SC); DTIC + IFN-alpha + Ta1 (6.4 mg SC); DTIC + Ta1 (3.2 mg SC); and DTIC + IFN-alpha (control group; n=97); repeated q4w; max 6 cycles; DTIC was given at a dose of 800 mg/m^2 IV on D1, Ta1 was given on D8-11 and 15-18, and IFN-alpha as 3 MU SC on D11 and D18; Ta1 (Zadaxin, SciClone Pharmaceuticals)	Assess whether Ta1 could potentiate the efficacy of DTIC (with or without IFN-alpha) in the treatment of metastatic melanoma	Ten and 12 tumor responses were observed in the DTIC + IFN-alpha + Ta1 (3.2 mg) and DTIC + Ta1 (3.2 mg), respectively, versus four in the control group, which was sufficient to reject the null hypothesis that $P \leq 0.05$; overall response rate was numerically higher in subjects treated with any Ta1 vs control but was not statistically significant; median OS was 9.4 months in subjects given Ta1 vs 6.6 months in the control group but was not statistically significant	These results suggest Ta1 has activity in subjects with metastatic melanoma and provide rationale for further clinical evaluation of this agent.
Danielli et al. 2018	Retrospective chart review; Italy	61 subjects with unresectable metastatic melanoma (stage III and IV) who	Ta1 doses not reported	Evaluate the potential additive effect of using sequentially Ta1 and anti-CTLA-4 mAbs in subjects	Among subjects treated with Ta1, 21/61 received anti CTLA-4 inhibitors and Ta1; median OS at the data cut off	This is the first report on long-term follow-up of Ta1-treated patients.

Author	Design	Population	Treatment	Objective	Results	Author Conclusion
		received Ta1 (from Maio et al. 2010 study) and a compassionate use (EAP) program and 95 subjects who received ipilimumab		affected by metastatic melanoma	was 57.8 and 7.4 months in subjects treated sequentially with Ta1 and anti-CTLA-4 inhibitors or Ta1 alone respectively; in the second analysis median OS at the data cut off was 38.4 and 8 months in subjects treated with Ta1 and ipilimumab or ipilimumab alone respectively	Moreover, an advantage in OS in patients sequentially treated with Ta1 and ipilimumab was seen that suggests a synergistic effect.

Abbreviations: CR = complete response; CTLA-4 = cytotoxic T lymphocyte-associated protein 4; DTIC = dacarbazine; IL-2 = interleukin-2; IFN = interferon; MU = million units; PR = partial response; OL = open label; OS = overall survival; R = randomized

APPENDIX 2: HCC STUDIES

Author	Design	Population	Treatment	Objective	Results	Author Conclusion
Stefanini et al. 1998	Single arm, single center; Italy	12 subjects with HCC who were selected for TACE	TACE + Ta1 900 μg/m^2 BIW SC for 6 months. TACE procedure consisted of iodized oil mixed with doxorubicin followed by embolization with Spongel pellets or Gelfoam pellets	Evaluate the use of Ta1 associated with TACE for the treatment of HCC	TACE + Ta1 resulted in a longer survival when compared to historical control group who were treated with TACE alone. OS rates not provided.	The absence of toxicity and favorable effects observed in this open study call for a double-blind control study to confirm the efficacy of the combined treatment.
Shuqun/Cheng et al. 2004	RCT ("randomly divided into three groups based on the date of admission"), single center; China	57 subjects with HCC	Hepatectomy plus TACE and Ta1 (thymalfasin, SciClone Pharmaceuticals) postop (1.6 mg SC BIW x 6 months) (A) (n=18); hepatectomy plus TACE postop (B) (n=23); or hepatectomy only (C) (n=16). TACE procedure was performed 1.5 months after hepatectomy with a solution containing carboplatin, epirubicin HCl, and mitomycin suspended in iodized oil.	Anti-recurrence effects of TACE with Ta1 postoperatively for patients with HCC after hepatectomy	No differences in the recurrent rate; but "recurrent time" was 7.0, 5.0, and 4.0 months in groups A, B, and C. Median survival was 10.0, 7.0, and 8.0 months for groups A, B, and C.	Comprehensive therapy combining TACE plus Ta1 postop could not decrease the recurrent rate, but it might delay the recurrent time and prolong survival periods for HCC pts after hepatectomy.
Cheng et al. 2005[1]	Prospective, non-randomized controlled trial, single center; China	70 subjects with resectable HCC and evidence of chronic HBV DNA	Hepatectomy only (n=35) or hepatectomy plus Ta1 (thymalfasin, SciClone Pharmaceuticals) (1.6 mg SC BIW x 6 months from the first week after hepatectomy) and lamivudine (100 mg per day x 2 years from the second week after hepatectomy) postop (n=35)	Report the preliminary results of the potential efficacy of antivirus therapy using lamivudine and Ta1 in reducing the recurrence and prolonging the survival of HCC patients accompanying with chronic hepatitis B infection with active virus replication after undergoing hepatectomy	Median "recurrent time" was 10.0 vs 6.5 months and median survival time was 12.5 vs 6.0 months in the treatment and control groups respectively.	Antivirus therapy using lamivudine and Ta1 postoperatively may suppress the HBV reaction, delay the recurrent time and prolong the survival for HCC patients coexisting chronic HBV infection with active virus replication.
Gish et al. 2009	Phase 2 RCT; USA	25 subjects with unresectable HCC	TACE plus Ta1 (thymalfasin) (1.6 mg SC 5 times weekly; n=14) or TACE alone (n=11) x 24 weeks. TACE with doxorubicin or cisplatin	Compare TACE plus Ta1 with TACE alone for unresectable HCC; designed primarily as a safety study	8/14 (57.1%) vs 5/11 (45.5%) in the TACE plus Ta1 group vs TACE only were responders. Median OS was 110.3 and 57.0 weeks for the	In patients with unresectable HCC, TACE + Ta1 resulted in numerically higher rates of survival and tumor

Author	Design	Population	Treatment	Objective	Results	Author Conclusion
			(according to participating site's guidelines).		TACE plus Ta1 group vs TACE only. Differences for these endpoints did not reach statistical significance.	response, including transplant candidacy, with fewer bacterial infections, than TACE alone. Treatment regimens for HCC including Ta1 as an immunomodulator should be evaluated in larger trials.
Liang 2016	Retrospective, single center study with propensity score matching; China	558 subjects with HBV associated HCC who were treated with radical hepatectomy (106 pairs after matching)	Ta1 1.6 mg SC BIW x 6 months (n=146) or radical hepatectomy only (n=412)	Retrospectively evaluate the impact of Ta1 therapy on outcomes in HCC pts after radical hepatectomy	The 1-, 2- and 3-year OS rates were 87.2, 82.0 and 68.4% in the Ta1 group and 78.2, 64.2 and 49.7% in the historical control group. The 1-, 2- and 3-year recurrence-free survival rates were 79.7, 70.8 and 67.3% in the Ta1 group and 69.9, 61.5 and 51.6% in the historical control group.	These results suggest that post-hepatectomy Ta1 therapy improves liver function and significantly prolongs recurrence-free and OS in subjects with HBV-associated HCC.
He 2017	Retrospective cohort study, single center; China	206 subjects with HCC who underwent liver resection	Unclear; per article "current regimen" of Ta1 (Zadaxin) is 1.6 mg SC BIW for at least 26 weeks (n=44) or resection only (n=162)	Evaluate the efficacy of Ta1 as an adjuvant therapy in subjects with small HCC who underwent liver resection	The 1, 3, and 5-year OS rates were 97.7, 90.6, and 82.9% in the Ta1 group and 95.1, 80.5, and 62.9% in the resection only group. The 1, 3, and 5-year RFS rates were 70.5, 56.8, and 53.3% in the Ta1 group and 65.8%, 41.3%, and 32.1% in the resection only group.	Ta1 as an adjuvant therapy after liver resection may improve the prognosis of small HCC patients after liver resection.
Zhou 2018	Retrospective, single center; China	36 subjects with advanced HCC who do not fit the UCSF criteria and underwent liver transplant	Sirolimus, huaier granules, and Ta1 (Zadaxin, SciClone Pharmaceuticals) ("16 mg" SC per day x 10 days, and then BIW [unclear how long Ta1 was administered]) (n=18) or tacrolimus-based therapy (n=18)	Investigated the effectiveness of a combined therapy based on sirolimus, Ta1, and huaier granules for liver transplant pts with advanced HCC	The 1, 3, and 5-year OS rates were 100, 94.4, and 77.8% in the sirolimus, Ta1, and huaier granule group and the 1-year OS rate was 77.8% in the tacrolimus-based group. None of the subjects in the tacrolimus-based group lived over 2 years post-LT. The 1, 3, and 5-year DFS rates were 88.9, 55.6, and 50.0% in the sirolimus, Ta1, and huaier granule group and the 1-year	SRL+ (sirolimus with Ta1 and huaier granules) therapy appears to be safe and effective in preventing HCC recurrence following liver transplant with no significant adverse events and warrants further investigation.

Author	Design	Population	Treatment	Objective	Results	Author Conclusion
					DFS rate was 22.2% in the tacrolimus-based group.	
Linye et al. 2021	Retrospective, single center study with propensity score matching; China	468 subjects with HBV-related HCC after curative resection (100 pairs after matching)	Ta1 1.6 mg SQ BIW for at least 6 months after resection (n=228) or resection only (n=240)	Evaluate the efficacy of Ta1 as adjuvant therapy in subjects with solitary HBV-related HCC who underwent curative liver resection	The 1, 3, and 5-year OS rates were 98.0, 86.4, and 55.5% in the Ta1 group and 95.0, 71.5, and 47.2% in the resection only group (HR 0.0542, 95% CI 0.324-0.908). The 1, 3, and 5-year RFS rates were 92.2, 73.1, and 58.2% in the Ta1 group and 84.7, 62.2, and 32.6% in the resection only group (HR 0.517, 95% CI 0.317-0.842).	Our study demonstrated that Ta1 as an adjuvant therapy could delay recurrence and prolong OS for patients with solitary HBV-related HCC after curative resection.

Abbreviations: BIW = twice a week; HBV = hepatitis B virus; HR = hazard ratio; LT = liver transplant; OS = overall survival; RFS = recurrence-free survival; TACE = transarterial chemoembolization

1. Shuqun et al. (2006), titled "Antiviral Therapy Using Lamivudine and Ta1 for Hepatocellular Carcinoma Coexisting with Chronic Hepatitis B Infection," appears to be an interim analysis of the same study population.

APPENDIX 3: INFECTIONS AFTER HSCT STUDIES

Author	Design	Population	Treatment	Objective	Results	Author Conclusion
Perruccio 2010	Single arm, single center; Italy	8 sibling HLA matched and 6 haploidentical[1] HSCT recipients	Sequential cohorts of subjects received Ta1 (1.6 mg once daily SC for 16 weeks) starting from day +40, +20, and +1 after transplantation	Determine the safety and efficacy of Ta1 in recipients of HSCT for hematologic malignancies	No cases of acute or chronic GVHD. Observed improvement in polymorphonuclear and dendritic cell functions, increased T-cell counts, and earlier appearance of functional pathogen-specific CD4+ and CD8+ T cell responses (by a sensitive limiting dilution assay that detects frequency of T cells specific for ***Aspergillus***, ***Candida***, CMV (cytomegalovirus), ADV (adenovirus), VZV (varicella zoster virus), HSV (herpes simplex virus), ***Toxoplasma***) when compared to historical control haploidentical transplant recipients.	At this very early stage of the clinical trial, we conclude Ta1 administration is safe and may impact favorably on immune function.
Ding 2013	RCT, single center; China	7 allogeneic HSCT and 1 autogenetic HSCT recipients	Ta1 (SciClone Pharmaceuticals) 1.6 mg SC BIW for 4 weeks (n=4) or standard of care; subjects were given anti-infection therapy according to the results of imageology and etiology	Investigate the effect of Ta1 administration in infective recipients of HSCT for hematologic malignancies	No cases of acute or chronic GVHD in the Ta1 group. Observed increases IFN-γ, IL-2, IL-10, and IL-12 after one month in the Ta1 group vs the control group.	Ta1 administration is safe and may impact favorably on immune function, and that it may improve resistance to infection and induce immunotolerance without GVHD.

Abbreviations: BIW = twice a week; GVHD = graft-vs-host disease; HSCT = hematopoietic stem cell transplantation; HLA = human leukocyte antigen

1. Haploidentical is a term used to describe a tissue donor whose HLA tissue type partially matches (usually 50%) the HLA tissue type of a person receiving a stem cell or organ transplant. HLAs are a set of cell surface markers found on a person's cells and tissues that play an important role in the body's immune response to foreign substances. Before someone receives a transplant, their HLA tissue type will be matched with that of a potential donor. A haploidentical donor, such as a parent, child, or sibling, may be used in a stem cell or organ transplant when a fully or closely matched donor is not available. See https://www.cancer.gov/publications/dictionaries/cancer-terms/def/haploidentical-donor, Accessed June 5, 2024.

Thymosin Alpha 1 (Ta1) – Related Bulk Drug Substances (Ta1 (free base) and Ta1 acetate) Nomination

Company Name	**Wells Pharmacy Network**
Contact Name	**Anthony Campbell, PharmD, BCSCP**
Contact Phone	**352-622-2913**
Contact Email	**ACampbell@wellsrx.com**

503A Bulk Drug Substance Nomination	
What is the name of the nominated ingredient?	Thymosin Alpha-1
Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in 207.3 (a)(4)?	YES
Is the ingredient listed in any of the three sections of the Orange Book?	FDA approved orphan drug status https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=132600
Were any drug monographs for the ingredient found in the USP or NF monographs?	NO
What is the chemical name of the substance?	**IUPAC Name:** N-Acetyl-L-seryl-L-alpha-aspartyl-L-alanyl-L-alanyl-L-valyl-L-alpha-aspartyl-L-threonyl-L-seryl-L-seryl-L-alpha-glutamyl-L-isoleucyl-L-threonyl-L-threonyl-L-lysyl-L-alpha-aspartyl-L-leucyl-L-lysyl-L-alpha-glutamyl-L-lysyl-L-lysyl-L-alpha-glutamyl-L-valyl-L-valyl-L-alpha-glutamyl-L-alpha-glutamyl-L-alanyl-L-alpha-glutamyl-L-asparagine **IUPAC Condensed:** 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 **Sequence**: SDAAVDTSSEITTKDLKEKKEVVEEAEN **InChIKey** NZVYCXVTEHPMHE-ZSUJOUNUSA-N $C_{129}H_{215}N_{33}O_{55}$
What is the common name of the substance?	Thymlafasin, Zadaxin, Thymosin Alpha-1
Does the substance have a UNII code?	W0B22ISQ1C
What is the chemical grade of the substance?	Provided by FDA Registered Supplier/COA
What is the strength, quality, stability, and purity of the ingredient?	Assay, Description, Solubility, etc.; Example of Certificate of Analysis for this chemical is attached.
How is the ingredient supplied?	Solution for Injection

Is the substance recognized in foreign pharmacopeias or registered in other countries?	**European Medicines Agency** **https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu302110** **http://crdd.osdd.net/raghava/thpdb/display_thppid_sub.php?details=Th1110**
Has information been submitted about the substance to the USP for consideration of drug monograph development?	YES
What dosage form(s) will be compounded using the bulk drug substance?	Subcutaneous Injectable
What strength(s) will be compounded from the nominated substance?	3mg/mL
What is the anticipated route(s) of administration of the compounded drug product(s)?	Subcutaneous Injection
Are there safety and efficacy data on compounded drugs using the nominated substance?	Chien RN, Liaw YF. Thymalfasin for the treatment of chronic hepatitis B. *Expert Rev Anti Infect Ther*. 2004;2(1):9-16. doi:10.1586/14787210.2.1.9 Qiu SJ, Zhou ZG, Shen F, et al. A multicenter, randomized, observation-controlled clinical trial to evaluate the efficacy and safety of thymalfasin adjuvant therapy in patients with HBV-related HCC after curative resection - first announcement of the protocol. *Expert Opin Biol Ther*. 2015;15 Suppl 1:S133-S137. doi:10.1517/14712598.2015.1039979 Yu Y, Tian JH, Yang KH, Zhang P. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue*. 2009;21(1):21-24. Wolf E, Milazzo S, Boehm K, Zwahlen M, Horneber M. Thymic peptides for treatment of cancer patients. *Cochrane Database Syst Rev*. 2011;2011(2):CD003993. Published 2011 Feb 16. doi:10.1002/14651858.CD003993.pub3 Wang FY, Fang B, Qiang XH, et al. The Efficacy and Immunomodulatory Effects of Ulinastatin and Thymosin α1 for Sepsis: A Systematic Review and Meta-Analysis. *Biomed Res Int*. 2016;2016:9508493. doi:10.1155/2016/9508493 Maio M, Mackiewicz A, Testori A, et al. Large randomized study of thymosin alpha 1, interferon alfa, or both in combination with dacarbazine in patients with metastatic melanoma. *J Clin Oncol*. 2010;28(10):1780-1787. doi:10.1200/JCO.2009.25.5208 You J, Zhuang L, Tang BZ, et al. A randomized controlled clinical trial on the treatment of Thymosin a1 versus interferon-alpha in patients with hepatitis B. *World J Gastroenterol*. 2001;7(3):411-414. doi:10.3748/wjg.v7.i3.411

	You J, Zhuang L, Cheng HY, et al. Efficacy of thymosin alpha-1 and interferon alpha in treatment of chronic viral hepatitis B: a randomized controlled study. *World J Gastroenterol*. 2006;12(41):6715-6721. doi:10.3748/wjg.v12.i41.6715 Chien RN, Liaw YF, Chen TC, Yeh CT, Sheen IS. Efficacy of thymosin alpha1 in patients with chronic hepatitis B: a randomized, controlled trial. *Hepatology*. 1998;27(5):1383-1387. doi:10.1002/hep.510270527 Schulof RS, Lloyd MJ, Cleary PA, et al. A randomized trial to evaluate the immunorestorative properties of synthetic thymosin-alpha 1 in patients with lung cancer. *J Biol Response Mod*. 1985;4(2):147-158. Andreone P, Cursaro C, Gramenzi A, et al. A double-blind, placebo-controlled, pilot trial of thymosin alpha 1 for the treatment of chronic hepatitis C. *Liver*. 1996;16(3):207-210. doi:10.1111/j.1600-0676.1996.tb00729.x Zheng BX, Cheng DY, Xu G, Fan LL, Yang Y, Yang W. [The prophylactic effect of thymosin alpha 1 on the acute exacerbation of chronic obstructive pulmonary disease]. Sichuan Da Xue Xue Bao Yi Xue Ban. 2008 Jul;39(4):588-90. Chinese. PMID: 18798500.
Has the bulk drug substance been used previously to compound drug product(s)?	YES
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	May be used in conditions requiring immune response modulation (e.g.): *Hepatitis B & C* *Cancer – non-small cell lung (NSCLC), hepatocellular, malignant melanoma* *Chemotherapy adjunct* *Chronic inflammatory conditions; autoimmunity* *Cystic fibrosis* *Lyme disease* *Depressed response to vaccinations; adjunct to flu vaccine* *Geriatric immune support*
What is the reason for use of a compounded drug product rather than an FDA-approved product?	no FDA-approved product available
Is there any other relevant information?	Added as an Attachment

References included with nomination FDA-2015-N-3534-0288

International Peptide Society (IPS) Professional Monograph – Thymosin alpha 1.

Tuthill, CW and King, RS. 2013. Thymosin Alpha 1 - A Peptide Immune Modulator with a Broad Range of Clinical Applications. Clin and Exp Pharmacology, 3(4). doi:10.4172/2161-1459.1000133.

Certificate of Analysis

Thymosin α1 Acetate

Product Name	: Thymosin α1 Acetate	**Lot No.**	: DL5532
Mfg. Date	: Mar 01, 2020	**Exp. Date**	: Feb 28, 2023
M.F.	: $C_{129}H_{215}N_{33}O_{55}$	**M.W.**	: 3108.3
CAS No.	: 62304-98-7	**Batch Qty**	: 315 g
Sequence	: 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		

TESTS	SPECIFICATIONS	RESULTS
Appearance	White to off-white powder	White powder
Identification	3108.3 ± 2	3108.6
Solubility	Soluble in water or 1% acetic acid at a concentration of ≥1mg/mL to give a clear, colorless solution	Conforms
Water Content (KF)	≤ 5.0%	2.3%
Acetate Content	≤ 5.0%	3.3%
Peptide Purity (HPLC)	≥ 96.0%	98.3%
Assay (anhydrous; acetic acid free)	95 - 105%	98.0%
Conclusion: This product is a synthetic peptide and meets the specifications. Long Term Storage: Store in a sealed container at 2°C - 8°C in a fridge or freezer. Distributed by Darmerica.		

Note: Analytical results transcribed from the original COA provided by Chengdu Aoying Biotechnology Co., Ltd.; Lot No. TA2020001.

98 × 97.7 × 96.7% = 92.5%

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Based on the review of the above information, the lot stands released.

	Name	Title	Signature	Date
Prepared by	Sai Rasane	Quality Assistant		09/17/2020
Released by	Christina Boykin	Quality Assistant		09/17/2020