Guidance for Industry AL Amyloidosis — Developing Drugs for Treatment

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Guidance for More Efficient and Successful Drug Development Programs for AL Amyloidosis

I.   INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of medical products (ie, drugs and therapeutic biological products for humans) for the treatment of patients with immunoglobulin light chain (AL) amyloidosis. Transthyretin (ATTR) amyloidosis will be addressed in a separate guidance document.

This guidance is a result of collaboration between the US Food and Drug Administration (FDA) and the amyloidosis community. It is intended to serve as a focus for continued discussions among the FDA, pharmaceutical and biotechnology companies, sponsors, the academic community, and the patient and caregiver community. Early consideration of the topics addressed will enable sponsors to design more efficient and successful drug development programs.

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidance for Industry E9 Statistical Principles for Clinical Trials and Guidance for Industry E10 Choice of Control Group and Related Issues in Clinical Trials. This guidance focuses on specific medical product development and trial design issues that are unique to the study of AL amyloidosis.

AL amyloidosis is a disease consisting mostly of older adults (median age at diagnosis, 63 years) (Cohen and Comenzo, 2010; Merlini, 2011; Gertz, 2011). The disease has also been diagnosed in patients in the third decade of life but not in patients younger than age 18. Therefore, this guidance will not address pediatric populations.

The FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, they describe the FDA's current thinking on a topic and should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. The use of the word "should" in FDA guidance means that something is suggested or recommended but is not required.

II.   BACKGROUND

The incidence of AL amyloidosis in the United States has been estimated at 9 cases per million person-years (PY) (95% CI, 5.1-12.8 cases per million PY) or approximately 1550 to 4000 new cases of AL amyloidosis annually in the United States (Kyle et al, 1992). Although more recent estimates (eg, 12.8 cases per million PY) exceed those from previous incidence assessments, this US incidence is likely a significant underestimate because of the well-recognized underdiagnosis and misdiagnosis of this disease.

AL amyloidosis is a rare, progressive, and lethal malignancy affecting mostly older adults (median age at diagnosis, 63 years); however, it is being diagnosed in an increasing number of younger persons (Lousada et al, 2015). AL amyloidosis is caused by a small B-lymphoid cell clone (usually from a plasma cell population) that produces excess monoclonal immunoglobulin free light chains (FLCs), which are structurally unstable (Cohen and Comenzo, 2010; Merlini, 2011; Gertz, 2011; Dispenzieri, 2012). These pathologic light chains (LCs) have a twofold effect: they misfold, aggregate, and deposit as fibrillar material in visceral organs and they have direct tissue toxicity. This leads to progressive end-organ dysfunction, organ failure, and ultimately death. Approximately one-third of patients with newly diagnosed AL amyloidosis die within 12 months of diagnosis despite treatment – a statistic that has remained unchanged for the past 25 years. Despite this statistic, median survival for AL amyloidosis has been improving for the past decade. A 2005 retrospective study of 209 newly diagnosed patients in Italy and 281 newly diagnosed patients at the Mayo Clinic found that the median survival was 2.5 years in the Italian group and 1 year in the Mayo Clinic group (Palladini, 2005a). Ten years later, a European collaborative retrospective study of 230 newly diagnosed patients treated with improved standard of care found that median survival was >5 years (Palladini, 2015).

The primary goal of therapy for these patients is improvement of end-organ function. All parts of the amyloidogenic pathway represent potential treatment targets: chemotherapy agents directed toward the clonal plasma cells, small molecules that impact the pre-fibrillar light chains, and agents that aim to directly accelerate removal of soluble toxic light chains and the amyloid fibril deposits from tissues (Dispenzieri et al, 2015; Weiss, 2016). The aim of treatment is: (1) to reduce or eliminate monoclonal immunoglobulin FLC, which can potentially halt the progression of organ damage and improve organ function (Dispenzieri et al, 2012) and inhibit further deposition, and (2) to clear existing amyloid to more directly ameliorate organ dysfunction. Therapies directed at the former goal have formed the bulk of treatment strategies in recent decades. Measures that can help patients achieve better hematologic responses will lead to better organ responses and would have a significant impact on overall

survival (OS). Therapies directed at existing amyloid may have direct impact on organ responses and also have a significant impact on OS.

Prognosis is determined by the extent of organ impairment, especially cardiac dysfunction, and the depth of response to therapy. Current staging criteria (Kumar et al, 2012) assess the cardiac proteins troponin and N-terminal fragment of the pro-brain natriuretic peptide (NT-proBNP) and also assess FLC levels. NT-proBNP is the strongest measure of functional cardiac response. In interventional studies, it has been predictive of patient survival after treatment despite differences in patient populations, types of treatment, and treatment schedules.

In AL amyloidosis, the invariable compromise of vital organ function causes major decrements in patient quality of life. Patient-reported outcomes and other quality-of-life assessments are therefore particularly relevant endpoints. The complex multiorgan nature of this disease make such assessments critically important in assessing the impact of therapy.

No drugs for AL amyloidosis have received FDA approval, and this represents a major unmet medical need. It is important to facilitate the development of medical products that have the potential to be more effective, less toxic, or both for patients with this rare and fatal disease. In the absence of approved therapies, medications authorized for multiple myeloma (MM) are often used off label for the treatment of AL amyloidosis (Comenzo 2009; Dispenzieri, 2015; Wechalekar, 2015).

A. Existing Treatment Landscape

Patients with AL amyloidosis have complex treatment needs. They require therapeutic interventions that stop the production of amyloid-forming LC, that provide supportive care for organ dysfunction, and that remove existing amyloid deposits to potentially limit and reverse organ dysfunction. The development of treatments to meet each of these needs will make a unique and noninterchangeable contribution to improving patients' quality of life and survival.

No treatments for systemic AL amyloidosis have received US regulatory approval. However, plasma cell–directed agents approved to treat MM (alkylating agents, proteasome inhibitors, corticosteroids, and/or immunomodulatory drugs, either as single agents or in combination) are being used off label in the treatment of AL amyloidosis. A few specific plasma cell–directed and amyloid fibril-directed agents are in development. The National Comprehensive Cancer Network (NCCN) guidelines provide an alphabetical list of available agents for the primary treatment of AL amyloidosis, yet they recommend that patients should be treated in a clinical trial when possible because

existing data on available agents are insufficient to indicate optimal treatment for the disease (NCCN 2015). The best long-term outcomes are reported with high-dose chemotherapy and autologous peripheral blood with stem cell transplantation, but this aggressive regimen is only an effective treatment modality in the approximately 20% of highly selected patients who are sufficiently fit to tolerate it. Most other patients are treated with combination chemotherapy (usually with a combination regimen containing a proteasome inhibitor). Treatment-related adverse events and mortality remain a concern with all current therapies for AL amyloidosis. There is substantial variability in the effectiveness and safety of these therapies. In the absence of approved therapies, treatment choices are based on the patient's age, extent of organ involvement, and pace of disease progression, with ongoing response monitoring using biomarkers of hematologic and cardiac responses. The final determinant is often regimen-related toxicity (Dispenzieri et al, 2012; Merlini 2011) and, given the lack of robust evidence, is often tempered by the physician's perception about the efficacy and toxicity of available therapies. There is a fine balance between chosen treatment regimen and treatment-related toxicities in patients with multiorgan AL amyloidosis.

None of the current therapies are curative. Hematologic relapse and organ relapse occur even after response to the first line of therapy. Patients typically receive multiple therapies over the course of their disease to keep the clonal makers suppressed, support end-organ function, and extend survival. No randomized trials have been completed in the past 15 years (as of October, 2016), though the first randomized study reported interim analysis data at the International Symposium on Amyloidosis in July 2016 (Palladini et al, ISA 2016) and is ongoing. Current data consist of retrospective studies or small, prospective, often single-arm and single-institution trials, all using differing regimens and all potentially affected by selection or referral bias. Given the lack of data and the rarity of AL amyloidosis, consensus is lacking regarding the agents that should be used for patients with either newly diagnosed or relapsed/refractory AL amyloidosis.

III.   DEVELOPMENT PROGRAM

A. General considerations

1.   *Working with the FDA in developing drugs for AL amyloidosis*

- The FDA recognizes the difficulties inherent in studying rare diseases such as AL amyloidosis and has 4 established programs to facilitate and expedite the development and review of serious conditions: fast-track designation, breakthrough therapy designation, accelerated

approval, and priority review designation. These mechanisms are explained in the "Guidance for Industry, Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014."

- General considerations for developing drugs and biologics for rare diseases are outlined in "Rare Diseases: Common Issues in Drug Development Guidance for Industry, DRAFT GUIDANCE, June 2015." Given the prevalence of AL amyloidosis, sponsors may consider applying for orphan drug designation to offset development costs and provide 7 years of marketing exclusivity.

- In addition, sponsors are encouraged to meet with the Agency often to discuss their development program.

  2.   Clinical pharmacology considerations

- AL amyloidosis is often associated with renal or hepatic impairment, or both; thus, it is important to define the appropriate dose of the drug for patients with impaired renal or hepatic function. AL amyloidosis patients with severe nephrotic syndrome may have altered protein binding, which could affect free drug levels. In AL amyloidosis clinical trials, appropriate dose modifications may be required for patients with renal or hepatic impairment to ensure that their drug exposures are similar to those of patients without renal or hepatic impairment.

- Patients with AL amyloidosis may have cardiac involvement and be predisposed to cardiac arrhythmias; thus, the relevance and feasibility of a preclinical cardiovascular (CV) safety study should be considered before the start of a phase 1 study. Results from nonclinical CV assessments may help in evaluating the need for clinical assessments (eg, concentration-QT_C analysis to determine proarrhythmic risk) and in considering treatment class.

- Requirements for approval of standard clinical pharmacology studies should be weighed with relevance to the class of the product and the life-threatening nature of the disease. It may be that some studies can be deferred until after approval, or perhaps even waived, if the patient population and metabolic pathways of the drug, considered together, suggest a low likelihood of clinically meaningful pharmacokinetic (PK) effects.

- Exposure-response relationships can also attest to the effectiveness of confirmatory studies. The response variables used in the analyses may include prespecified primary and secondary endpoint(s) and results involving biomarkers collected in the studies for efficacy and safety.

3. Safety considerations

Safety considerations must take into account the often fragile physical state of patients with AL amyloidosis.

The most widely used therapeutic approaches for AL amyloidosis, as well as some in development, include cytotoxic or immunomodulatory drugs that are approved for other aggressive malignancies and are inherently toxic at therapeutic doses. The risks that these agents pose may be amplified in the AL amyloidosis patient population because these patients usually have at least one component of critical organ involvement even at the time of diagnosis. Further, "off-target" effects of specific chemotherapeutic or immunomodulatory drugs used or tested in AL amyloidosis (cardiotoxicity, nephrotoxicity, or neurotoxicity) might be expected to exacerbate the cardiac dysfunction, renal failure, or neuropathy common to patients with AL amyloidosis.

Treatment of patients with AL amyloidosis using current plasma cell–directed agents is generally associated with greater treatment-related toxicity than is seen in patients with MM (Comenzo et al, 2002; Jaccard et al, 2007; Moreau et al, 1998) when the same agents directed at plasma cell dyscrasia are used. There is a conflict between the greater toxicity in patients with AL amyloidosis and the need to produce a rapid response (Wechalekar et al, 2015; Palladini, 2005b; Dispenzieri, 2010; Tapan, 2010).

The use of an Independent Review Committee (IRC) charged with regularly monitoring safety data from all studies and empowered to suspend or terminate the trial if a significant safety signal is found is highly recommended to ensure the safety of trial participants.

4.   Early-phase clinical development considerations

- Phase 1 study of PK, safety, and tolerability should be conducted in patients to establish dose.

- Rather than conducting a separate phase 2 study, patients could be enrolled in expansion cohorts, as an extension of a phase 1 study, in order to further explore tolerability and preliminary efficacy signals and to either refine or define the patient populations for pivotal studies.

- The initiation of a prospective natural history study in the early phase of development can be useful for comparison and helpful in later design of a pivotal study.

- Early characterization of the PK and identification of appropriate doses or dose and schedule for patients with either renal or hepatic impairment can be conducted in phase 1 expansion cohorts or as stand-alone special population studies before the initiation of phase 2 or phase 3 clinical trials.

    5. *Patient population*

To distinguish AL amyloidosis from other amyloidoses, biopsy diagnosis of AL amyloidosis should be used for study eligibility, using current clinical criteria (NCCN 2015): (1) histochemical diagnosis of amyloidosis based on Congo red staining of histologic sections with exhibition of an apple-green birefringence when viewed under polarized light; (2) amyloid typing ICH/IF or mass spectroscopy is strongly suggested and is necessary if clinical and laboratory parameters are insufficient to establish a diagnosis of AL amyloidosis, or if the diagnosis is in doubt; and (3) rarely, gene sequencing from genomic DNA for mutated genes that can cause hereditary forms of amyloidosis.

AL amyloidosis is a rare disease and the study population is heterogeneous. The study population for clinical trials may be defined based on criteria including newly diagnosed, relapsed or refractory disease, degree of organ involvement and involved organs, hematologic stability with persistent organ dysfunction, and patient status before or after chemotherapy.

The major study populations include untreated patients with new diagnoses, patients who respond to initial plasma cell–directed therapy, and patients with relapsed/refractory disease. Refractory hematologic disease is the absence of hematologic response to initial therapy or relapse within 60 days of last dose (Comenzo et al, 2012). Refractory organ disease is the absence of organ response, despite treatment. The presence of severe cardiac disease assessed by biomarkers has become an exclusion criterion for many efficacy trials of initial therapy (or therapy in the relapsed/refractory setting). This practice effectively divides the study population with new diagnoses into 2 subpopulations: those with and those without advanced cardiac disease. Inclusion/exclusion criteria and study objectives should be carefully considered in the trial design relative to the population chosen for study.

Efficacy studies require a patient population in whom clinical improvements can be quantified (functional assessments and biomarkers). Quantitative assessment of hematologic responses requires differential FLC (dFLC) levels ≥50 mg/L at the time of study entry. Patients with hematologic-evaluable disease are easier to define in the new diagnosis setting. In the relapsed disease setting, there is no consensus on when therapy should be resumed (Milani ISA 2016).

Because patients with advanced heart failure in the context of AL Amyloidosis are prone to sudden death, they are poor candidates for clinical trials of standard agents. Eligibility criteria often exclude patients with NT-proBNP levels above a certain threshold (ie, >8500 ng/L) or with advanced New York Heart Association Functional Classification stages of heart failure (Wechalekar, 2013).

These multiple inclusion/exclusion criteria eliminate a high percentage of patients with AL amyloidosis from clinical trials. Even in the setting of relapsed or refractory disease, the requirement for dFLC levels ≥50 mg/L eliminates up to 30% of patients, NT-proBNP levels >650 and <8500 ng/L also may limit 30% of patients from clinical trials, and a history of chronic kidney disease can exclude additional patients. Sponsors nevertheless are encouraged to include as broad a range of patients as possible in clinical trials in this rare disease, limiting eligibility restrictions by including only those needed for assessment of the specific endpoints of the trial. It is recommended that the trial include clinically significant and quantifiable organ involvement, such as, but not limited to, cardiac, renal, nerve, or hepatic. These disease inclusion criteria should be based on biomarkers, clinical measures or imaging. However, as mentioned earlier, clinical trial design consideration should include appropriate powering and patient stratification so that efficacy and safety signals will not be obscured.

6. *Efficacy considerations*

The conduct of laboratory tests, for both safety and efficacy (biomarker) endpoints, by a central laboratory at late stages of development is highly encouraged.

A requirement for central independent assessment may be applicable to clinical endpoints, such as hospitalization or radiologic response for which adjudication is essential, and should be decided on a trial-by-trial basis.

B. **Specific Efficacy Trial Considerations**

1. *Study design*

[Refer to "ICH Harmonized Tripartite Guidance: General Considerations for Clinical Trials E8," 1997.
(http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073132.pdf)]

Single-Arm studies

Randomized controlled trials are preferred in drug development. However, given the rarity of AL amyloidosis, the unmet medical need, and the existence of biomarkers such as NT-proBNP, plasma FLC, and proteinuria, which can demonstrate objective improvement, single-arm studies that evaluate the effects of investigational agents on biomarkers can be considered for accelerated approval. Accelerated approval may be granted if improvement in these biomarkers is greater than has been observed with other therapeutic interventions in a similar AL amyloidosis population or greater than expected based on disease progression demonstrated in natural history studies (21 CFR 314, subpart H; 21 CFR 601, subpart E).

[Refer to "Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics," 2014. (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf)]

A nested, single-arm study in AL amyloidosis within, for example, a controlled myeloma or generic anti-amyloid trial may provide preliminary safety, efficacy, and dosing information to inform subsequent trials.

Controlled trials

[Refer to "Guidance for Industry: E 10 Choice of Control Group and Related Issues in Clinical Trials," 2001. (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073139.pdf)]

- Randomization and blinding

In general, a randomized controlled trial design is preferred for registration-enabling studies. For studies of anti-plasma cell–directed agents, the control arm would likely include therapeutically active regimens. For studies of anti-amyloid therapies, the control arm may include a placebo because there are no amyloid directed treatments currently available for use in a control arm. Single-blinding may also be considered. Early guidance and advice should be sought from the agency.

- Stratification factors

The heterogeneity of the AL amyloidosis population makes stratification across arms an important consideration in efficacy trials for both newly diagnosed and relapsed/refractory disease. Potential stratification parameters can include, but are not limited to, the severity of

cardiac risk (eg, by Mayo staging, cardiac risk stage 1 vs stage 2 vs a subgroup of cardiac risk stage 3 (3b generally excluded)), newly diagnosed versus previously treated, exposure to specific previous therapies/agents, and number of previous regimens.

- Historical or active control arm

The use of historical controls in AL amyloidosis should stringently involve assurances that the control is directly relevant to the population in the study. Historical control use may be limited by the heterogeneity of the population and by the lack of prospective, multicenter studies. Eligibility criteria differ widely, and efficacy data are generally not presented as intention-to-treat. In addition, many studies include populations with both newly diagnosed and relapsed/refractory disease. Identifying a suitable, matched historical population to serve as a control may therefore be problematic. Discussion with the agency on the selection of historical controls is highly recommended to ensure that appropriate selection criteria are considered matched compared with those in the clinical trial.

- Superiority trials

The preferred design for efficacy trials in general is a parallel, randomized, controlled superiority trial using a therapeutically active regimen in the control arm. In the case of AL amyloidosis, this trial design is complicated by the absence of an approved therapy to serve as a comparator, and by the paucity of prospective trials in this disease to provide efficacy data to enable accurate power calculations.

Superiority trials of new investigational agents can make use of an add-on design if the medical product is intended as adjunctive treatment. An add-on trial of this type would enable evaluation of drug effects in the context of commonly used medical products in AL amyloidosis.

The effect size of the comparator must be identified to define the superiority margin (21 CFR 314.126). This may be problematic because of the lack of large prospective, multicenter trials of the many regimens used in AL amyloidosis. Another consideration is the inherent variability in outcome and the response in different AL amyloidosis subpopulations.

- Noninferiority study design

 noninferiority design may be appropriate to evaluate efficacy because of the need to use an active therapeutic regimen in the control arm in trials in AL amyloidosis, for which there are no approved therapies. In the absence of approved therapies, sponsors should engage early with

FDA to determine if off-label standard of care (SOC) treatment could serve as a control for a noninferiority trial.

The FDA "Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics" (2014) notes that when available therapy exists for a condition, a new treatment generally would be considered to address an unmet medical need if the treatment: (1) provides efficacy comparable to that of available therapy while avoiding serious toxicity that occurs with available therapy, avoiding less serious toxicity that is common and causes discontinuation of treatment of a serious condition, or reducing the potential for harmful drug interactions; or (2) provides safety and efficacy comparable to those of available therapy but has a documented benefit, such as improved compliance, that is expected to lead to an improvement in serious outcomes. The FDA Guidance for Non-Inferiority Clinical Trials (Mar 2010) should be consulted.

To use a noninferiority design, the effect size of the comparator in the new study must be identified to define the noninferiority margin (21 CFR 314.126). This may be problematic because of the lack of large prospective, multicenter trials of the many therapies tested in AL amyloidosis. An inferiority trial may prove difficult in this rare population because inferiority trials usually require a larger sample size. Another consideration is the inherent variability in outcome and the response in different subpopulations. Sponsors considering a noninferiority design should discuss the design with the appropriate review division before trial initiation.

- Single-agent or combination therapy

As mentioned, patients with AL amyloidosis require therapies that produce both hematologic and organ responses. Different combinations of chemotherapeutics may yield the largest hematologic response. The treatment of patients with combinations of different classes of therapy (plasma cell–directed plus amyloid-directed agents) may be considered.

  o Single-agent trials of anti–plasma cell therapies provide a clear signal of the activity and safety of an investigational agent. Although single agents, often cytotoxic drugs (frequently combined with dexamethasone), are used in the treatment of AL amyloidosis, the therapeutic trend is moving toward the use of combinations of drugs with different mechanisms of action (eg, a proteasome inhibitor plus an alkylating agent plus dexamethasone) in patients healthy enough to tolerate the additional toxicity to improve therapeutic response. The clinical evaluation of Investigational agents may occur in combination with other (albeit unapproved) therapies that represent the SOC for AL amyloidosis treatment.

- Investigational agents that do not directly target the malignant plasma cells (eg, drugs targeting the end-organ fibril deposition) may be used concurrently with another drug regimen targeting the plasma cell.
- Single-agent trials of anti-amyloid or amyloid-directed therapies may also be proposed in patients who are hematologically stable, but continue to have organ dysfunction.

2. *Study population*

Ideally, the study population should be as broad as possible for a rare disease, with selection of the appropriate endpoint for the population to be studied. Eligibility criteria should be appropriate for the endpoint but should avoid being unnecessarily restrictive. Further, quantifiable disease should be required for certain endpoints. Sponsors should consult the FDA Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products (Dec 2012).

3. *Primary efficacy endpoints (frequency of assessment)*

3.1. Biomarkers and surrogate endpoints

The use of a clinical endpoint such as OS extends clinical trial durations, which is especially problematic for a rare disease. Considering that many patients with amyloidosis live longer than 5 years after diagnosis and that only a subset of patients survive fewer than 2 years, conducting a survival trial to completion may take many years for this very small patient population. In addition, there is a subset of patients within those who may be too far advanced for therapeutic intervention due to sudden cardiac death. Finding a patient population to study for a survival endpoint and enrolling that population may be especially challenging. Biomarkers can assist in the development and evaluation of therapies for AL amyloidosis by serving as surrogate primary endpoints for survival. The biomarker should support a hypothesized mechanism of action by serving as a marker in pharmacodynamic (PD) studies or by suggesting an appropriate dose or duration of action (Biomarkers Definitions Working Group 2001). In some cases, biomarkers are used to define risk or identify potential responders to a treatment; this biomarker may be reflected in the prescribing information (Biomarkers Definitions Working Group 2001).

Surrogate endpoints are a subset of biomarkers expected to predict clinical benefit (or harm or lack of benefit) and are intended to substitute for a clinical endpoint (Biomarkers Definitions Working Group 2001). The FDA has established a process for qualifying drug development tools, including biomarkers, intended for potential use, over time, in multiple drug development programs ["Guidance for Industry and FDA Staff: Qualification Process for Drug Development

Tools", 2014.
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf)]. Although no known biomarker in AL amyloidosis has been formally qualified as a surrogate endpoint, FLC and/or NT-proBNP response to treatment has been shown to predict clinical outcome and survival, and both are clinically validated.

Current standards of care and consensus guidelines for the treatment of patients with AL amyloidosis make essential the integration of biomarker endpoints into clinical trials. Physicians routinely use biomarkers to monitor the efficacy of a therapeutic regimen and to make decisions regarding when to change therapeutic strategies without waiting for clinical deterioration that is frequently irreversible. Patients in a clinical trial may therefore be withdrawn from the study before a clinical endpoint is reached on the basis of no change in or deterioration of biomarkers, reduced exposure to the toxicity of ineffective therapy, and possible switch to effective therapies.

The international consensus organ and hematologic response criteria apply to patients with newly diagnosed disease. Response to these biomarkers, however, has been proven to predict increased survival in patients with relapsed or refractory disease as well (Merlini, et al 2016). Use of the response criteria for hematologic, cardiac, (Palladini et al, 2012) and renal disease (Palladini, et al 2014) may be considered endpoints for clinical trials of all phases in all study populations (Comenzo et al, 2012). Efficacy of the primary endpoint should be reported on an intention-to-treat basis.

3.1.1. Use of Biomarkers as Single Primary Outcome Measures

For a biomarker to serve as a surrogate endpoint, a body of reliable evidence that the biomarker is likely to predict clinical benefit is essential. Full approval of a drug with a biomarker as a single primary surrogate efficacy outcome measure may be granted if the biomarker is formally qualified through the FDA process. Accelerated approval of a drug with a biomarker as a single primary surrogate efficacy outcome measure may also be granted, even if the biomarker is not formally qualified, but likely to predict clinical benefit.

[Refer to "Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics," 2014.
(http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf)]

For AL amyloidosis, both FLC levels and NT-proBNP have been shown to predict survival and may be considered for use as primary endpoints.

- Hematologic response by serum FLC assessment

Hematologic response, determined by changes in FLC level, is an important endpoint in AL amyloidosis and is acknowledged to serve as a predictor for long-term survival benefit (Palladini et al, 2012). Complete response (CR) is defined by international consensus criteria as negative serum and urine immunofixation results and normal FLC ratio. Partial response is defined as a 50% reduction in difference between involved and uninvolved serum free light chain levels (dFLC). Very good partial response (VGPR) is defined as dFLC <40 mg/L (Palladini et al, 2012).

The decrement in pathologic FLC levels (defining hematologic response) produced by therapeutic intervention directly predicts survival in AL amyloidosis (Palladini et al, 2012) in a mode proportional to the depth of the FLC response (CR, VGPR, PR). This is based on data from a number of independent studies that have matured in the past 20 years, including patient populations with both newly diagnosed and relapsed/refractory disease (Dispenzieri et al, 2006, 2012; Kastritis et al, 2010; Kumar et al, 2011a; Lachmann et al, 2003; Mahmood et al, 2014; Palladini et al, 2012, 2013, 2014; Reece et al, 2014; Wechalekar et al, 2007, 2013). A pivotal study by Palladini et al, 2012, found a strong and statistically significant correlation between reduction in FLC and improvement in OS at both a 3-month and a 6-month landmark analysis. Responses for patients were as follows: CR, 2.5 deaths/100 PY; VGPR, 9.0 deaths/100 PY; PR 14.7 deaths/100 PY. Nonresponders had 51.4 deaths/100 PY. These data taken together suggest that the early-response assessment can predict long-term survival outcomes for patients with newly diagnosed AL amyloidosis. Hematologic response, specifically CR rate, has been accepted as a primary endpoint for accelerated approval of plasma cell–directed agents.

- Cardiac response measured by serum NT-proBNP

The AL amyloidosis research community has summarized the evidence for NT-proBNP as a surrogate endpoint for clinical outcome/survival (Merlini 2016).

The presence and extent of cardiac involvement is the major prognostic determinant (Dispenzieri et al, 2004). Cardiac failure results from the combined effects of the mass action exerted by amyloid deposits and by the direct cardiotoxicity of amyloid light chains. These misfolded proteins activate the p38α mitogen-activated protein kinase (MAPK) pathway, resulting in oxidative stress, impaired calcium homeostasis, and, eventually, cardiomyocyte death (reviewed in Merlini et al, 2016). Activation of the p38α MAPK pathway results in increased production of NT-proBNP through a transcriptional upregulation of the pre-pro protein (Koivisto, et al 2011), thus providing a robust pathogenic link for this biomarker. Criteria were developed and validated by an international working group of experts to assess cardiac response and progression using NT-proBNP and are being used by experts worldwide to

monitor patients' cardiac responses to treatments. Cardiac response to treatment, or progression of cardiac involvement, is defined as a decrease or an increase, respectively, in NT-proBNP of 30% and ≥300 ng/L. A patient's baseline NT-proBNP level must be greater than 650 ng/L to qualify as evaluable for response (Palladini et al, 2012). In contrast to NT-proBNP, Echocardiography, which had been one of the most important tests for cardiac involvement in patients with AL amyloidosis, has low sensitivity to assess interventional benefit (Dispenzieri et al, 2012; Palladini et al, 2012) and cardiac magnetic resonance imaging (CMR) has yet to be shown to be an effective measure of therapeutic response.

Independent studies in almost 2000 patients using differences in study design, treatment regimens or combinations of treatment regimens, treatment class, patient population, and geographic location consistently demonstrated that NT-proBNP response to treatment reflects changes in cardiac function and predicts survival in patients with AL amyloidosis (Kastritis et al, 2010; Palladini et al, 2006, 2010; Wechalekar et al, 2013). Further, NT-proBNP levels can predict survival in patients with similar hematologic responses (Wechalekar et al, 2013). Hematologic response in the absence of organ response results in a shorter survival time as compared to those patients achieving an organ response (Kaufman et al, 2015). For the subset of patients who achieve cardiac response after hematologic response, cardiac response occurs very quickly after hematologic response. Preliminary analysis of the outcome of the prospective, randomized phase 3 study comparing melphalan-dexamethasone with melphalan-dexamethasone-bortezomib shows that cardiac response, evaluated using NT-proBNP changes, is significantly associated with improved survival (Palladini et al, ISA 2016). This is the first prospective study to clinically validate the use of NT-proBNP as a surrogate, and it confirms the previous findings from retrospective studies. Based on the clinical validation, NT-proBNP may serve as a useful primary endpoint for trials in AL Amyloidosis for patients with cardiac involvement.

3.1.2. Use of Biomarkers as Supportive Secondary Outcome Measures

Secondary biomarker outcome measures may support a primary clinical outcome or primary biomarker outcome measure in several ways. One possible use is to support a label indication for a population broader than the primary population studied. An example is a therapy evaluated in a subgroup of the patient population such as cardiac AL amyloidosis patients that has positive evidence on a secondary biomarker outcome that measures function in another organ, such as proteinuria for renal impairment or alkaline phosphatase for hepatic impairment.

The kidney, like the heart, is an organ commonly involved in AL amyloidosis. To be evaluable for renal response assessment, a patient must have >0.5 g protein/24 h. A collaborative work between the Italian and the German amyloidosis centers has recently defined and validated criteria for renal response. Renal response is defined as a decrease in proteinuria by ≥30% or below 0.5 g/24 h without a 25% decrease in glomerular filtration rate. Renal response defined by these criteria has been demonstrated to result in longer renal survival as measured by time to dialysis in test and validation cohorts (Palladini et al, 2014a).

Although certain renal response criteria (eg, serum creatinine) can be assessed each cycle, other parameters (eg, 24-hour urine protein excretion) are assessed less frequently. Renal responses can lag behind hematologic responses by 6 to 12 months and can occur incrementally in the course of treatment (Comenzo et al, 2012; Palladini, 2014a; Kaufman, 2015). The duration of a study must be sufficient to capture the temporal range of renal responses, and patients should be followed for ≥12 months. Renal response should be used only as a supportive or secondary endpoint for plasma cell–directed therapies. For amyloid-directed therapies, renal response endpoint may occur more rapidly due to potential for direct removal of toxic amyloid from the kidney. In a recent study with an investigational amyloid directed therapy, median time to renal response was 4 months (Gertz ISA 2016). Therefore, renal response may be appropriate for use as primary endpoint for amyloid directed therapies for AL amyloidosis with renal involvement.

In patients with AL amyloidosis, amyloid may also affect the liver. No biomarkers are clinically validated to measure liver response and prognosis, but alkaline phosphatase has recently been studied in a small population without cardiac involvement and was prognostic for survival. Further, in the subset of this population with stage 1 AL amyloidosis, progressive liver involvement emerged as a significant cause of death and was predicted by elevated alkaline phosphatase (Palladini, 2014b). Alkaline phosphatase should be used only as a supportive or secondary endpoint for patients with liver involvement.

3.2. Clinical endpoints

- Overall survival

OS is often considered the gold standard by which to judge the merits of a particular experimental medication. OS for patients with AL amyloidosis is variable and is determined primarily by the extent of major organ involvement. OS as an endpoint for registration studies may not be practical for an ultra-rare disease such as AL amyloidosis. A survival endpoint requires more patients and significantly more time both to recruit patients and to reach the

endpoint. The current standard approach to treat AL amyloidosis is to use medications approved for multiple myeloma in an off-label setting. In terms of the treatment of patients with relapsed or refractory disease, it is common for patients to sequentially receive 5 or more different therapeutic regimens. Patients might also have been treated with novel, amyloid-directed agents. Subsequent therapies confound the analysis of OS in studies of investigational agents in patients with newly diagnosed disease and in those in early relapse, reducing the value of OS as a primary clinical endpoint.

Patients with less severe cardiac involvement (eg, those with stage 1, 2, or stage 3a cardiac involvement) may live for >3 years or significantly longer. Those patients with advanced heart failure (stage 3b) may have limited survival, but may be too far advanced for therapeutic intervention due to sudden cardiac death. In addition, there must be a path for approval for those with primarily noncardiac deposition of amyloid, such as patients with renal, nervous system, or gastrointestinal-predominant disease, who may live for 7 years before dialysis and who have an OS of >10 years. The length of time required for trials with survival as an endpoint significantly affects the ability to extend new treatments to patients.

There is precedence to approve new oncologic medications based on surrogate endpoints for survival, including progression-free survival and response rate. Other plasma cell–based diseases that are similar to AL amyloidosis (eg, MM and Waldenström macroglobulinemia) have received approval by the FDA using data generated in single-arm uncontrolled studies that have alternative endpoints rather than OS as an endpoint. Consultation with the FDA is strongly recommended when considering alternative endpoints for regulatory approval other than OS.

- Organ deterioration, progression, and mortality rate

Organ deterioration can be assessed functionally and using biomarkers, as discussed earlier, or by assessing hospitalization required by organ dysfunction. A novel composite clinical endpoint, using cardiac or renal markers, or mortality as an event (whichever occurs first), assessed within a specific window of time after randomization, can serve as an endpoint for full approval in a registration trial. A similar composite clinical endpoint, using only cardiac deterioration and mortality as events, can also serve as an endpoint for full approval. A cardiac deterioration event may be defined as hospitalization required for decreasing cardiac function, intravenous application of diuretic medication, or both. Renal deterioration may be defined as end-stage renal failure, requiring either dialysis or renal transplantation. When considering these types of endpoints, differences in standard of practice between sites should be addressed to ensure consistency in the determination of which patients meet the criteria for the novel endpoint. Other confounding variables to take into account in global studies are the difference in

standard practice for overnight hospitalization of patients. The use of an IRC to adjudicate these endpoints is recommended. These composite clinical endpoints may be able to assess both the morbidity and the mortality engendered by this disease. There are limitations to these composite clinical endpoints. In the case of a cardiac composite endpoint, the most clinically acceptable measure would be hospitalization for heart failure or any significant cardiac event (such as arrhythmia or acute coronary syndrome). In addition, in AL Amyloidosis, there is currently a dearth of information on hospitalization rates as the majority of patients are seen in tertiary centers and hospitalizations occur locally. This introduces challenges to predicting the rate of hospitalizations for powering clinical trials. However, the incorporation of biomarkers of organ function may be useful in this regard. Consultation with the FDA for designing novel composite clinical endpoints is strongly recommended and can incorporate a methodology for designing a weighted composite endpoint approach.

- Progression-free survival

Progression-free survival (PFS), based on biomarkers, has served as a primary endpoint for registration in related plasma cell malignancies, such as multiple myeloma. Assessment of progression is more complicated in AL amyloidosis, however. Clinicians commonly use hematologic biomarkers (FLC levels, ratios, and immunoelectrophoresis), cardiac biomarkers (NT-proBNP), and renal biomarkers (proteinuria or serum creatinine, or creatinine clearance) as evidence of disease progression. Evidence of progression in any of these biomarkers can drive treatment decisions. The criteria for progression in each of these parameters are defined by the Consensus Guidelines (Palladini et al, 2012). In addition, patients may receive salvage therapy before observed progression of disease because the minimum goal of therapy is considered to be VGPR or better, especially for patients with extensive cardiac involvement (Mahmood et al, 2014). Patients with PR, for example, may receive subsequent therapy before disease progression, which would result in the patient being censored from a primary PFS analysis. Sponsors are encouraged to prospectively evaluate PFS using consensus criteria and to establish a correlation between PFS and survival, or other clinical endpoints, to validate PFS as a primary endpoint for future registration studies. In addition, sponsors are encouraged to specify criteria and circumstances in which salvage therapy may be introduced before observation of PD to avoid confounding, which would result from uncontrolled application of a subsequent line of anti-amyloid therapy.

The strong statistical correlation between hematologic response or organ response and OS over many clinical studies suggests that hematologic PFS or organ PFS, as defined by consensus criteria, in combination with a trend for an increase in OS or improvement in other clinical

endpoints, such as quality of life, may constitute an appropriate endpoint for full approval (Palladini et al, 2012).

The composite clinical endpoint defined in section III B3 serves as a clinical event–based PFS endpoint.

- Quality of life

Improvement in quality of life, as measured by patient-reported outcomes, may serve as a clinical endpoint for full approval dependent upon psychometric validation of the instrument in AL amyloidosis. If there is an instrument that may be useful, the sponsor should consider including patient-reported outcomes in early-phase development as a secondary or exploratory endpoint. In designing a new instrument, using portions of already established instruments, such as the Short Form 36 General Health Survey (SF-36) or the European Organisation for Research and Treatment of Cancer Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity scale, should be considered, and the sponsor should begin to build a body of evidence to support the use of the HRQoL scale in AL Amyloidosis.

Publications on quality of life in AL amyloidosis have been limited, but a study published by Seldin et al, 2004 showed that improvement in the SF-36 after stem cell transplantation predicted an increase in OS, and a study by Caccialanza et al, 2012 reported that nutritional status independently affected SF-36 scores in patients with AL amyloidosis. Other studies, such as nonobservational studies, online registries, and qualitative and quantitative survey studies, can be used to validate and support these measures. Sponsors are encouraged to seek advice from the FDA's Clinical Outcome Assessment Qualification Program early in the course of clinical development.
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualification Program/ucm284077.htm

Please refer to Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, Dec 2009.

- Other clinical endpoints

Cardiac:

The 6-minute walk test (6MWT) is a measure of walking ability and may serve as a measure of improvement in cardiac function and multisystem disorders. More published data on AL amyloidosis are needed to ascertain the value of the test as a primary endpoint. If used in

clinical studies, the 6MWT must be standardized across all study designs to ensure consistency of the data reporting of this measurement.

Renal:

In renal clinical trials, the historical standard has been to use the combined endpoint of end-stage renal disease (ESRD) or loss of 50% of baseline estimated glomerular filtration rate (eGFR). Using ESRD alone is impractical because with most renal diseases the amount of loss of eGFR per year would take too long for significant outcomes to be observed in the standard 3- to 5-year studies. Most recently, the FDA has adopted two new endpoints 1) the combined endpoint of progression to ESRD or loss of 40% of baseline eGFR and 2) the progression to CKD stage 4 or 5.

Renal survival, defined as time from diagnosis to date of initiation of long-term dialysis, with death a competing risk, may be a useful clinical endpoint for patients with renal-predominant disease. To date, renal survival has not been used as a clinical endpoint for FDA drug approval. As discussed, many patients with renal-predominant disease can often experience renal survival periods of several years, which may make this endpoint difficult to reach in a trial. Nevertheless, dialysis is a life-altering intervention with considerable implications on morbidity, mortality, and patient quality of life.

Neuropathy:

Neuropathy impairment score of the lower limbs (NIS-LL), a measure of lower limb peripheral neuropathy, and *Neuropathy impairment score +7 (NIS+7)*, an additional measure of peripheral nerve function, may serve as useful primary endpoints for patients with disease-related peripheral neuropathy. Sponsors should note that the proteasome inhibitor bortezomib, which is frequently used in the treatment of AL amyloidosis, can cause neuropathy and may confound neuropathy endpoint measurements.

Liver:

The measure of liver size using computed tomography or magnetic resonance imaging may serve as a useful primary endpoint in patients with predominant liver involvement. Consensus guidelines for response and progression recommend using serum levels of alkaline phosphatase and liver CT to assess hepatic involvement (Gertz 2005; Comenzo et al, 2012), but have not been validated.

Other organs:

A subset of patients with AL amyloidosis has related gastrointestinal disease, localized amyloidosis (eg, tracheobronchial), and soft tissue involvement (often in eyes or tongue). Sponsors are encouraged to include them in studies whenever possible. One complication is the lack of endpoints that might be used to evaluate treatment response in these patients. The amyloidosis community and sponsors are encouraged to continue to develop endpoints that may be studied in these patients.

4. *Statistical considerations*

- Primary analysis, alpha control

Applied statistical analysis depends on the endpoints and outcomes of interest. For endpoints such as PFS and OS, the statistical test usually is the time-to-event analysis using log-rank test or Cox regression. Subsequent therapies may confound the interpretation of study results, such OS endpoints. Appropriate sensitivity analyses may be prespecified. Overall type 1 error should be controlled for the primary endpoint or for several endpoints with appropriate adjustment for multiplicity.

- Statistical designs

A draft guidance for selection of specific populations is available ("Guidance for Industry Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products, 2012" http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf). As noted earlier, sample size calculated based on conventional superiority trial design may be difficult to achieve in practice because of the rarity of the disease, and the trial might not be powered sufficiently to accurately assess efficacy. A single-arm study that meets a minimal clinical treatment effect can be sufficient under this circumstance, when background rates for the endpoints are known. A noninferiority trial design might also be considered but, again, may be difficult to conduct because of the rarity of the disease and the small patient population. An adaptive design may be used based on the FDA draft guidance titled "Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics." Other trial designs, such as Bayesian adaptive design using historical controls, may be used with the FDA's agreement based on the support of statistical theoretical proof and simulations. We encourage sponsors to work with the FDA to develop the most efficient and time-sensitive study designs possible to accelerate drug development for drugs that are likely to have clinical benefit.

5. *Safety*

There is no specific minimum number of patients who should be studied to establish the safety of a treatment (safety population) for any rare disease, including AL amyloidosis. Because AL amyloidosis patients often have various levels of involvement affecting different organs, the population studied in AL amyloidosis trials may be extremely heterogeneous. This lack of uniformity makes it difficult to analyze safety signals and complicates attribution of toxicities. The number of patients in the safety database is determined on a case-by-case basis. Taken into consideration may be the magnitude of benefit provided, the nature of the toxicities, the length of treatment, the size of the patient population who stands to benefit after marketing approval, and the overall quality of the data (eg, comprehensiveness and quality) (Rare Diseases: Common Issues in Drug Development. Guidance for Industry. DRAFT GUIDANCE).

For therapies that are intended for long term use (eg maintenance therapy), recognition of delayed toxicities is critical. Particular attention should be paid to the frequency and severity of known toxicities and to newly identified toxicities over the course of therapy with a particular agent. This information may influence the size of the safety database.

If there is concern about rare but serious adverse events (eg, from the mechanism of action or from experience with similar drugs or therapeutic biologic products in humans), a postmarketing trial may be needed to gather additional safety information.

6. *Risk-benefit considerations*

When conducting a benefit-risk assessment for a drug to treat such a life-threatening and rare illness, patients may accept greater risks if the treatment offers an advantage over available therapy (21 CFR 312.84, subpart E and 601, subpart E). A patient-focused drug development meeting held by the Amyloidosis Research Consortium in November 2015 underscored that patients are willing to accept some significant risks in return for a treatment that slows or stabilizes disease progression (The Voice of the Patient Report, June 2016). Evaluation of "risk" involves an assessment of the therapy's safety profile using "all tests reasonably applicable" to establish its use in the intended patient population (Rare Diseases: Common Issues in Drug Development Guidance for Industry, DRAFT GUIDANCE, June 2015). In AL amyloidosis, the risk of a particular therapy may vary according to clinical factors (eg, cardiac stage). Assessment of a therapy's potential benefits involves an appraisal of the effect of the medical product on all aspects of the disease process, including hematologic and organ response rates, health-related quality of life or changes in surrogate markers.

IV. REGULATORY REVIEW

As presented in section III A1, several mechanisms are available to shorten the time frame for review by the agency. These are fast-track designation, breakthrough designation, accelerated approval, and priority review.

A. Accelerated Approval Considerations for Drugs and Therapeutic Biological Products in Humans (Subpart H and Subpart E)

For serious or life-threatening conditions, such as AL amyloidosis, a new drug (21 CFR part 314, subpart H) or therapeutic biologic (21 CFR part 601, subpart E) for use in humans can be approved on the basis of adequate and well-controlled trials that establish that the drug or therapeutic biologic has an effect on a surrogate endpoint "that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence to predict clinical benefit" (21 CFR 314.510 and 21 CFR 601.40). Full approval would be contingent on required postmarketing clinical trials to verify the clinical benefit.

Two potential surrogate markers—FLC and NT-proBNP—are undergoing evaluation for use as a means for accelerated approval.

B. Full Approval

In the case of accelerated approval, conversion to full approval based on an endpoint that demonstrates clinical benefit is a postapproval requirement. It is advantageous to have this protocol designed and the trial *initiated* before filing for accelerated approval to ensure that the subsequent licensure does not interfere with the ability to complete the confirmatory clinical trial. One adequate and well-controlled trial may be sufficient for full approval in this population.

Given the limited number of available patients with AL amyloidosis, 2 successive primary endpoints can be assessed within the same trial. An interim analysis is conducted for the primary endpoint (eg, biomarker) for accelerated approval; patients then continue in the trial and are evaluated for the primary clinical endpoint for full approval. However, in these circumstances, appropriate controls must be in place to ensure that the assessment of the efficacy outcome obtained at the interim analysis does not inadvertently affect the conduct of the ongoing trial.

Accelerated approval may also be given to a subpopulation using a surrogate endpoint while the broader population is being assessed for full approval through a clinical endpoint.

V.   OTHER CONSIDERATIONS

Nonclinical

- Because of the serious and life-threatening nature of the disease, the recommendation is to follow the nonclinical testing strategy outlined in ICH S9, which applies to both small molecule and biotechnology-derived pharmaceuticals. According to the Rare Disease Draft Guidance, an abbreviated nonclinical study package may be considered. If an abbreviated plan is being considered, a pre–investigational new drug (IND) meeting should be held with the FDA to determine the adequacy of the nonclinical package.

- An exception to ICH S9 would be that, given the cardiac involvement of many patients with AL amyloidosis, CV safety pharmacology testing should be conducted before clinical trials are initiated (per ICH S7A and S7B); however, the limited number of relevant animal models is an important consideration. Additional dedicated pharmacology studies would not be required unless a specific risk has been identified.

- To support an IND in AL amyloidosis, reproductive toxicity studies do not need to be performed given the nature of the disease and the elderly patient population; however, embryofetal development toxicity (segment 2) studies should be performed before a marketing application is submitted. According to ICH S9, fertility and early embryonic development (segment 1) and prenatal and postnatal development (segment 3) studies would not be warranted. Consultation with the FDA is recommended to determine the acceptability of the nonclinical safety package before phase 3.

- The safe starting dose for first-in-human trials should be calculated in accordance with note 2 in ICH S9 (use of STD10 in rodent and HNSTD in nonrodent species).

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