CURE SMA

SCIENTIFIC CONSIDERATIONS FOR DRUG COMBINATIONS

THIS STATEMENT WAS PRODUCED IN PARTNERSHIP WITH THE CURE SMA INDUSTRY COLLABORATION.
THE MEMBERS OF THE CURE SMA INDUSTRY COLLABORATION ARE AVEXIS INC, A NOVARTIS COMPANY, ASTELLAS PHARMA INC, BIOGEN, CYTOKINETICS INC, GENENTECH/ROCHE PHARMACEUTICALS, AND SCHOLAR ROCK.

cure SMA

Make today a breakthrough.

OVERVIEW AND PURPOSE

SPINAL MUSCULAR ATROPHY

Spinal muscular atrophy (SMA) is a disease that robs people of physical strength by affecting the motor nerve cells in the spinal cord, taking away the ability to walk, eat, or breathe. SMA affects approximately 1 in 11,000 births, and about 1 in every 50 Americans is a genetic carrier.

Despite the devastating impact of this disease, there is now reason for hope. Thanks to the dedication of our community and the ingenuity of our researchers, there are now multiple treatments approved by the U.S. Food and Drug Administration (FDA) that target the underlying genetics of SMA.

But our work is not done. We need to develop and deliver additional therapies and approaches to treatment that push toward further breakthroughs, and continue to change the course of SMA for everyone affected—from infants to adults—until we find a cure.

With new treatments available for SMA, people are asking, "Can combining these therapies lead to better outcomes?" This question is especially relevant because of the different ways single therapies may impact individual patients as a result of many factors–including the patient's current age, age at the start of treatment, type, and stage of disease and severity of symptoms.

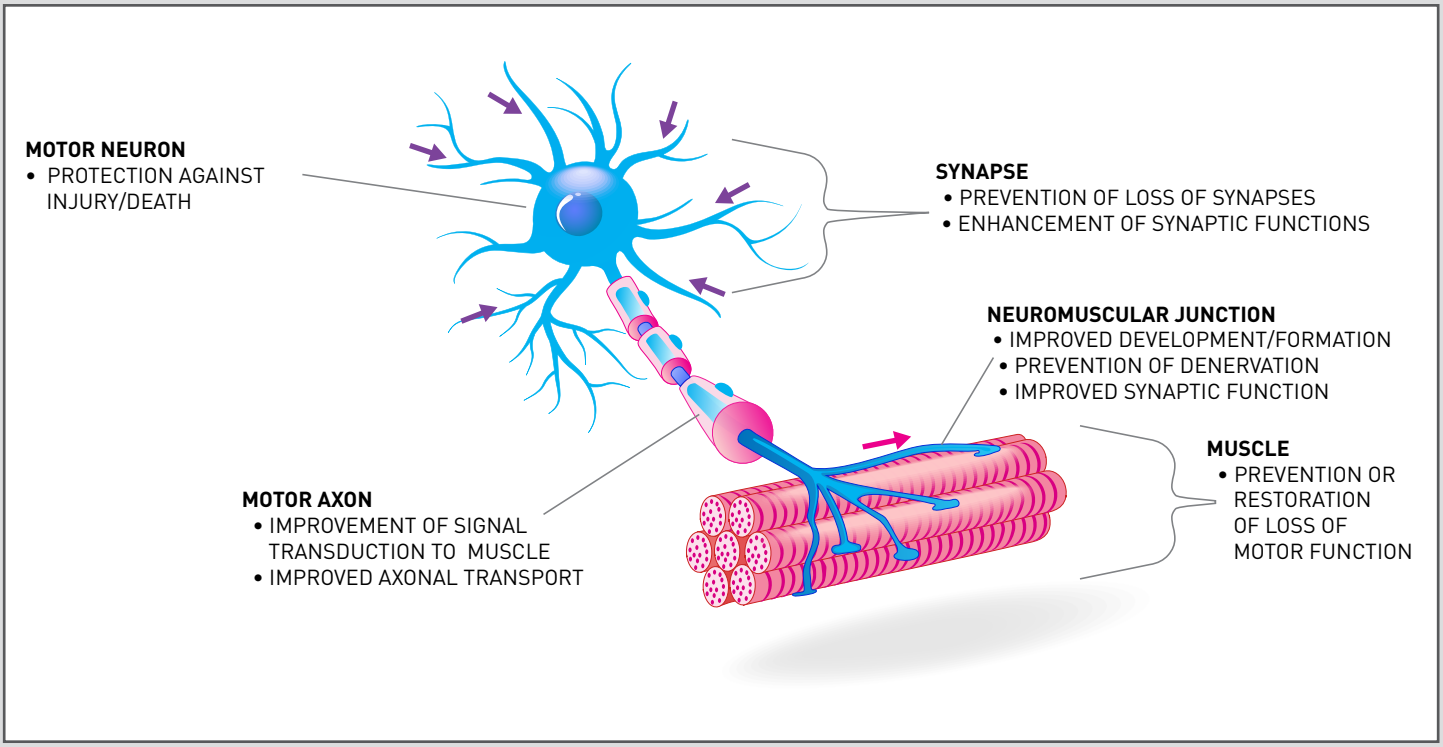
Cure SMA developed this Community Statement for families and caregivers to better understand the complex topic of combining treatments, including potential benefits and limitations. With this effort, we hope to provide a foundation upon which patients and families can work with their doctors to evaluate and pursue optimal treatment. As always, Cure SMA recommends patients consult with their healthcare providers regarding any treatment considerations or decisions.

SMA TREATMENT

PROGRESS, BUT UNMET NEED PERSISTS

There are multiple approaches being explored to treat SMA. This includes efforts to increase the amount of survival motor neuron protein (SMN) in the body by replacing or correcting the faulty SMN1 gene or modulating the low-functioning SMN2 "back-up gene." This type of therapy is called, "SMN dependent." A second approach, commonly called "SMN independent," aims to target other pathways, systems, and processes within the body. (See Figure 1, Table 1)

FIGURE 1: POSSIBLE POINTS OF THERAPEUTIC INTERVENTION DEFINED



Lower Motor Neuron: a nerve cell whose cell body is in the spinal cord and whose axon projects outside of the spinal cord to innervate and control muscles. Loss of lower motor neurons is considered a hallmark of SMA. **Motor Axon:** a long, slender projection neuron that conducts electrical impulses in order to transmit information to different neurons or muscles. **Synapse:** a structure that permits a neuron to pass an electrical or chemical signal to another neuron or to the target effector cell. **Neuromuscular Junction:** a chemical synapse formed by the contact between a motor neuron and a muscle fiber. It is at the neuromuscular junction that a motor neuron is able to transmit a signal to the muscle fiber, causing muscle contraction. **Muscle:** contains protein filaments of actin and myosin that slide past one another, producing a contraction that changes both the length and the shape of the muscle cells producing force and motion.

TABLE 1: THERAPEUTIC STRATEGIES

SMN DEPENDENT THERAPEUTIC STRATEGIES	SMN INDEPENDENT THERAPEUTIC STRATEGIES
Gene therapy Replaces the missing SMN1 gene via a viral vector	**Neuroprotection** Protects against neuronal injury or degradation
SMN2 promoter activation Causes the SMN2 gene to be "on" more, generating more fully functional protein	**Muscle enhancement** Prevents and restores loss of motor function
SMN2 splicing modulation Redirects splicing of SMN2 to make more full-length transcripts containing exon 7	**Neuronal function** Enhances neuronal transmission

The recent breakthroughs that have led to the FDA approval of multiple therapies have provided the SMA community with new options for treatment. However, given the many variables involved with SMA–including the varying age of onset and severity of symptoms and impact on activities of daily living–these therapies may not be appropriate or effective for all patients, and the type of administration and related safety issues can place significant burdens on patients and their families.

As real-world experience with these new treatments increases, we are learning more about how they work and in which disease settings and situations the treatments are most effective, as well as where there are still important gaps in available treatments.

For example, it appears that therapeutic intervention may be more effective when it occurs in the earliest stages of disease (including before symptoms are evident). This leaves a significant area of unmet need among patients with more advanced disease, who may need therapies targeted at symptoms in addition to those that are aimed at the underlying genetic driver of SMA.

As has been documented by the landmark Cure SMA Voice of the Patient Report[1] and survey activities, SMA patients have an array of serious unmet medical needs that must be addressed by treatment approaches. These include respiratory issues, problems with feeding, loss of mobility, inability to communicate, and distress, among others.

The concept of combining treatments stems from the potential to see added or synergistic benefit by addressing multiple aspects of the disease concurrently to improve outcomes for patients. Recent history is replete with examples where such combined or "cocktail" approaches have led to positive results across many serious diseases, including HIV, many types of cancer, and certain genetically driven conditions.[2, 3, 4]

Although there is no conclusive evidence yet, there is strong interest in the SMA community to explore whether such results can be seen in patients with SMA. This statement provides an overview of the opportunities, cautions, and limitations that should be considered when evaluating these approaches, beginning with forming a clear understanding of what is meant by the term "combination therapy."

[1] http://www.curesma.org/documents/advocacy-documents/sma-voice-of-the-patient.pdf

[2] https://www.eurekalert.org/pub_releases/2018-11/mali-cgt111318.php

[3] https://www.ncbi.nlm.nih.gov/pubmed/30937182

[4] https://www.nature.com/articles/s41434-019-0071-x

THE TERM "COMBINATION THERAPY"

DEFINED FOR SMA

The phrase "combination therapy" can be used to mean varying things across diseases and in different situations. Sometimes it is used to describe combining multiple treatment approaches. For example, this occurs in cancer treatment when chemotherapy is combined with radiation and/or surgery. The "combination therapy" phrase can also describe the process of using several types of drugs sequentially or in an alternating fashion, which occurs in some cancers when an immunotherapy is first used to prime a patient's immune system and then a chemotherapy or targeted therapy agent is administered shortly thereafter for a type of "one-two punch."

For the purpose of this statement, we define "combination therapy" to mean, "Two or more therapeutic agents (generally drugs or biologics)–working through the same or different mechanisms of action–that are used concurrently." It is important to keep in mind that some drugs may have effects for a long period of time after administration, such as gene replacement therapy. This definition of "simultaneous use" is meant to encompass drugs that may be administered only one time, but continue to have biologic effects in the patient.

COMBINATION APPROACHES TO TREATMENT

OVERVIEW

In the SMA community there is increasing interest in understanding whether combination therapy could improve outcomes, given the success of combining therapies in other diseases. There is increasing evidence of success with "cocktail" approaches to treating serious illness, including the use of the anti-retroviral AZT (azidothymodine) for HIV/AIDS [5] and multi-drug chemotherapy regiments like R-CHOP (rituximab [Rituxan], cyclophosphamide, doxorubicin hydrochloride, vincristine [Oncovin], prednisolone) for lymphoma. [6]

Additionally, in oncology, standards of care for multiple tumor types now include combinations across drug-based modalities, such as combined regimens of targeted therapy and immunotherapy. This progress has generated enthusiasm that a combination approach could work for other rare conditions, including SMA. For example, there is interest in determining whether combining a drug that upregulates SMN with a drug that enhances muscle function or neuroprotection might offer greater therapeutic benefit than one of the drugs alone.

A decision to combine therapies in any disease setting must be carefully considered, thoughtfully pursued, and based on a strong scientific rationale supported by evidence that suggests the combination will lead to improved outcomes that outweigh a potential increased risk. [7]

[5] https://www.niaid.nih.gov/diseases-conditions/antiretroviral-drug-development

[6] https://www.medicalnewstoday.com/articles/324261.php

[7] https://www.merckmanuals.com/home/cancer/prevention-and-treatment-of-cancer/combination-cancer-therapy

RISK-BENEFIT CONSIDERATIONS OF COMBINATION THERAPY

There are multiple issues that must be addressed, including balancing the potential benefit that might be derived from a combination therapy with the potential for increased safety risks. There is also a need to understand what additional costs may be incurred when using multiple therapies.

It is especially important to avoid assuming that combining treatments will always yield more benefit or improved outcomes. In fact, in some cases combining two or more therapies could lead to less efficacy and more negative side effects than might be achieved when using one of the treatments alone. Cases of marginal, if any, benefit and worse toxicity stemming from combining therapies have been reported in studies for a variety of diseases, including multiple types of cancer and rheumatoid arthritis. [8,9]

When evaluating the potential impact of a combination therapy approach, clinical studies will often compare outcomes from combined treatments to the use of a single treatment alone. Combinations generally are considered successful if they produce a better response together than each individual treatment would be expected to produce on its own. However, because treatment combinations can have additive or even synergistic effects caused by the chemical and biological interactions of the compounds, it is often the degree to which the combination improves upon outcomes that becomes most important in evaluating the promise of the approach.[10]

It is also important to note that effects of therapy will vary depending on the mechanism of action of the drug. In SMA, for example, using more than one drug aimed at upregulating the SMN protein may not have added benefit if a single drug can achieve the required threshold for maximal SMN impact on its own. On the other hand, combining an SMN upregulator with a different type of drug (e.g., a therapy aimed at improving muscle function) might be beneficial since the two therapies could have an additive positive impact.

Additional considerations for combining therapies involve timing of treatment and the progression of a patient's disease. For example, there are relevant questions to consider about how stages of disease (e.g., early vs. later stage) might impact the success of a combination therapy approach. This question comes up regularly when considering likely effectiveness of therapy (e.g., it is generally assumed that treating earlier in the course of disease can improve chances for a successful outcome), while there are additional nuances relating to potential increased risks and negative drug-drug interactions that are relevant in the specific context of combination therapy.

The remainder of this statement provides additional detail and context for these considerations in the context of SMA.

[8] https://ascopubs.org/doi/abs/10.1200/jco.2012.30.15_suppl.2572

[9] https://onlinelibrary.wiley.com/doi/pdf/10.1002/art.1780371012

[10] https://www.nature.com/articles/nm.4426

CONSIDERATIONS FOR COMBINATION THERAPY

SAFETY AND EFFICACY

IMPORTANCE OF EVALUATING SAFETY RISKS FOR COMBINATION THERAPIES

Using any type of therapy carries safety risks, which is why the FDA carefully reviews clinical data for all new drugs and biologics to ensure they can be used safely by the intended patient population. Once drugs are on the market, healthcare providers will generally use them according to their label indications and will be hesitant to combine single agents without evidence to support the safety of doing so.

Evaluating the safety of combining two or more approved therapies should be done in a clinical trial setting or through well-designed, real-world data collection protocols and registries, moving beyond understanding the safety profile of each therapy on its own. For example, there may be chemical or biological interactions among multiple treatments when they are administered concurrently. This has been reported in cases involving impact of one drug in a multi-drug "cocktail" on clearance of other drugs within the "cocktail," leading to worse outcomes.[12]

It is also possible that the known side effects of a single drug may be altered when that drug is used as part of a combination. This could lead to a worsening of the side effect profile or a different set of side effects.

There is much evidence from across disease settings and therapeutic approaches of drug-drug interactions,[13] so any approach that seeks to combine drugs for treatment of SMA must evaluate the specific safety profile and interaction potential of that combination. Route of administration should also be taken into consideration when assessing whether it is possible to safely administer two therapies concurrently.

[12] https://www.aafp.org/afp/2007/0801/p391.html

[13] https://www.pharmacytimes.com/publications/issue/2011/august2011/customization-of-drug-interaction-software

OTHER IMPORTANT CONSIDERATIONS

COVERAGE, REIMBURSEMENT, AND ACCESS

The process of developing effective combination therapies for SMA involves additional aspects beyond the scientific, clinical, and regulatory topics previously discussed. Additionally, there are important issues related to access and reimbursement for therapies that must be addressed.

When making coverage and reimbursement decisions, insurers rely on evidence generated through the research and development process, as well as data stemming from commercial use of a product (sometimes called real-world data). The collection of real-world data is an important component, in addition to data from clinical trials, in determining benefits and risks of drug combinations. If single therapies are combined for use, the process for making such decisions and ensuring access for patients becomes more complex. Payors will want to see clear evidence of the added benefit, as well as the safety derived from using two or more treatments at the same time.

Adding to the complexity, different payors may interpret data from the same studies differently, leading to differing coverage decisions. Families considering pursuing combination therapy should be aware of how doing so could impact them financially.

PATIENT AND CAREGIVER BURDEN

In addition to understanding the impact that concurrent use of multiple therapies can have on patient outcomes, there is also a need to evaluate and balance impact on the daily lives of patients and caregivers. Dosing, schedules for treatment, and route of administration related to a combination therapy approach must all be considered. Adding therapies could result in additional burdens on families, including missed school or work time. There is also the potential for additional burden on families associated with enhanced safety monitoring–above and beyond what is required for a single therapy–that might go along with combination treatments. These considerations should be weighed when pursuing a combination approach.

PRIORITY OF OBTAINING SINGLE DRUG APPROVAL

Finally, it is important to recognize that there are added complexities, including potential costs and logistical barriers, for companies developing therapies that may be under consideration for combination. As described above, the significant additional requirements for developing pre-clinical data, conducting the necessary clinical testing, pursuing regulatory review, and advancing commercialization and reimbursement activities are all relevant to a company's decision-making. These topics become more complex when the drugs being evaluated for combination are the products of two or more different companies, requiring eventual cross-company collaboration.

In SMA, where the current standard of care includes to use of approved SMN-enhancing drugs, it is logical that sponsors developing new SMN-enhancing drugs will prioritize securing single agent approval for their compound. Companies developing drugs with other types of mechanisms will need to consider whether to pursue single-agent approval first or how to appropriately design their trial to include patients currently using an SMN-enhancing drug. These approaches to leverage standards of care by combining approved therapies with novel agents that rely on a different mechanism of action are frequently seen in the oncology setting, where multiple clinical studies are evaluating the impact of two and three drug combinations with standard chemotherapy.

CONCLUSION

Cure SMA has a strategic goal of finding novel targets beyond SMN to develop therapies that will provide benefit for symptomatic patients, either in combination or alone. As we pursue this goal, we will consider all the elements discussed in this Community Statement. By outlining these considerations, we aim to help patients, families, and caregivers better understand potential options and evaluate some important issues.

Scientific and clinical advances leading to new therapies for SMA are providing improved outcomes and significant hope for our community, even as there remains significant unmet need for SMA patients. Understandably, there are questions about opportunities to leverage these new single agents by combining them for even more progress, improving outcomes for all stages of disease and patients at all ages. As described above, efforts to develop combination therapy approaches for SMA to address these opportunities should be based on a strong scientific rationale and should be pursued in the context of clinical studies to evaluate safety and efficacy.

[14] http://www.curesma.org/documents/advocacy-documents/sma-voice-of-the-patient.pdf

CURE SMA

Cure SMA is a non-profit organization and the largest worldwide network of families, clinicians, and research scientists working together to advance SMA research, support affected individuals/caregivers, and educate the public and professional communities about SMA.

Cure SMA is a resource for unbiased support. We are here to help all individuals living with SMA and their loved ones, and do not advocate any specific choices or decisions. Individuals and caregivers make different choices regarding what is best for their situation, consistent with their personal beliefs. Parents and other important family members should be able to discuss their feelings about these topics, and to ask questions of their SMA care team. Such decisions should not be made lightly, and all options should be considered and weighed carefully. All choices related to SMA are highly personal and should reflect personal values, as well as what is best for each individual and their caregivers.

Remember that your healthcare team and Cure SMA are here to support you. To continue learning, please see other available Care Series booklets:

- Breathing Basics
- Caring Choices
- Genetics of SMA
- Musculoskeletal System
- Nutrition Basics
- Understanding SMA

 twitter.com/cureSMA

 @curesmaorg

 facebook.com/cureSMA

 youtube.com/user/FamiliesofSMA1

 www.linkedin.com/company/families-of-sma

Last updated March 2020

925 Busse Road, Elk Grove Village, IL 60007
800.886.1762 • Fax 847.367.7623 • info@cureSMA.org • cureSMA.org