MIDWEST CEPAC
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AN ICER PROGRAM

Comparative Clinical Effectiveness of Patisiran and Inotersen for Hereditary Transthyretin Amyloidosis

Research Protocol

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Institute for Clinical and Economic Review

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

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Background, Objectives, and Research Questions

Background

Hereditary transthyretin amyloidosis (hATTR) is a condition caused by misfolding deposits of transthyretin (TTR), a protein that is present in all human serum. Genetic mutations can increase the likelihood of TTR misfolding into an insoluble beta-pleated sheet, which deposits in body tissues. hATTR produces a spectrum of clinical manifestations ranging from pure polyneuropathy to selective heart involvement, and affects at least 10,000 people worldwide.[1,2] Due to under-diagnosis, the true number is likely greater. There are three major forms of transthyretin amyloidosis, which are distinguished by their symptoms and the body systems they affect: 1) hereditary ATTR (hATTR) amyloidosis, formerly considered two separate conditions, familial amyloid polyneuropathy (FAP) and familial amyloid cardiomyopathy; 2) leptomeningeal amyloidosis, which primarily affects the central nervous system (e.g., stroke, seizures, dementia); and 3) wild type ATTR, formerly senile systemic amyloidosis.[3]

This review focuses on hATTR as the neurologic symptoms are among the most disabling, and promising new treatments are on the horizon. hATTR amyloidosis is a rare, progressive, and fatal hereditary disorder. Deposition of TTR-derived amyloid fibrils produces severe, disabling sensorimotor disturbances (loss of sensation, pain, muscle weakness and loss of ambulation) and varying degrees of autonomic, cardiovascular, gastrointestinal, renal, leptomeningeal and bowel or bladder dysfunction.[4] If untreated, death occurs approximately 10-15 years after onset of hATTR amyloidosis. The age at onset varies from the second to ninth decade of life, with a median survival of 5 –15 years. Researchers have estimated mean health care costs of 125,645€ ($154,819) per untreated patient.[5]

While there is no treatment available that reverses damage caused by amyloid deposits, there are treatments that may prevent or delay progression.[6] The liver produces almost all of the body's TTR. Therefore, liver transplantation, which removes the abnormal TTR, is one potential treatment. Limitations of this approach include transplant availability, disease progression following transplant, and substantial morbidity and mortality associated with transplant itself.

Diflunisal, a generic nonsteroidal anti-inflammatory drug (NSAID) which stabilizes transthyretin tetramers, is currently considered first-line treatment in the United States. Use of diflunisal to treat hATTR is off-label. In a randomized trial of 130 patients with symptomatic hATTR, diflunisal significantly reduced progression of neurologic impairment at two years and preserved quality of life compared to placebo.[7]

Tafamidis, a TTR stabilizer administered orally once daily, is the only medicine approved to delay disease progression in hATTR, and is approved in the European Union and several South American and Asian countries.[8-10] However, the US FDA did not approve its use during a filing in 2012, due to limited efficacy data.[11] In addition, there are two investigational agents currently under FDA review for hATTR: patisiran (Alnylam Pharmaceuticals) and inotersen (Ionis Pharmaceuticals). Patisiran is an RNA interference therapeutic.[12,13] Administered via IV infusion, patisiran suppresses the production of both mutant and nonmutant forms of TTR. Inotersen is an antisense oligonucleotide (ASO) that complements exactly the messenger RNA (mRNA) that encodes for TTR. A once weekly subcutaneous injection, inotersen binds the mRNA leading to degradation of TTR by RNAase. In Phase III clinical trials, both agents improved measures of neuropathy impairment, the primary study outcome. Secondary endpoints included modified body mass index (mBMI), the product of serum albumin concentration and BMI which correlates with survival in hATTR.[14] Measures of cardiac function were among exploratory outcomes in the trials.

As the first agents targeting the production of the protein inducing hATTR, clinical interest in the use of patisiran and inotersen is likely to be high. However, there may be uncertainties related to the translation of surrogate outcomes to longer-term clinical benefit, the durability of such benefit, potential harms of treatment, and the costs associated with the use of these medications. All stakeholders will therefore benefit from a comprehensive review of the comparative clinical effectiveness, safety, and economic impact of patisiran and inotersen relative to standard care for hATTR.

Objectives

The scope of this project was previously available for public comment and has been revised upon further discussions and input from stakeholders. In accordance with the revised scope, this project will assess both the comparative clinical effectiveness and economic impacts of patisiran and inotersen for the treatment of hATTR. The assessment aims to systematically evaluate the existing evidence, taking uncertainty into account. To that aim, two research components inform the assessment: a systematic review of the existing evidence and an economic evaluation. This document presents the protocol for the systematic review of existing evidence (i.e., the clinical review). Please see the model analysis plan (expected publication in early June 2018) for details on the proposed methodology and model structure for the economic evaluation.

Research Questions

To inform our review of the clinical evidence, we have developed the following research questions with input from clinical experts, patients, and patient groups:

- In patients with hATTR, what is the comparative efficacy, safety, and effectiveness of patisiran versus placebo and inotersen versus placebo in terms of changes in neurologic

function, cardiac function, ambulation, mortality, quality of life, adverse events, and other key outcomes?

PICOTS Criteria

In line with the above research questions, we defined the following specific criteria utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting and Study Design) elements.

Population

We will review evidence for adults ages 18 and older with hATTR.

Interventions

The full list of interventions is as follows:

- Patisiran (Alnylam Pharmaceuticals)
- Inotersen (Ionis Pharmaceuticals)

We developed this list of interventions with input from patient organizations, clinicians, manufacturers, and payers.

Comparators

We will compare each drug to placebo, as placebo was the comparator in clinical trials and reflects usual supportive care. Data permitting, we also intend to compare each of the agents to each other and to diflunisal.

Outcomes

The key outcomes of interest from clinical trials in this population include:

- Neurologic function (e.g., modified neuropathy impairment score +7 [mNIS+7] and neuropathy impairment score – weakness subscore [NIS-W]),
- Ambulation (e.g., familial amyloid polyneuropathy disease [FAP] stage and polyneuropathy disability [PND] score),
- Quality of life (e.g. 36-Item Short-Form Health Survey [SF-36]) and disease-specific health-related quality of life (e.g., Norfolk-Quality of Life-Diabetic Neuropathy [Norfolk-QoL-DN])
- Autonomic function (e.g., postural systolic blood pressure)
- Cardiac function (e.g., left ventricle mass, ejection fraction, and/or longitudinal strain)
- Mortality

We will also review evidence for one surrogate outcome of interest, modified BMI (mBMI), an intermediate outcome correlated with mortality.

Other outcomes of interest include:

- Treatment-related adverse events
- Rates of severe (Grade 3 or 4) adverse events
- Drug discontinuation due to adverse events
- Treatment-related deaths

Timing

Evidence on intervention efficacy, safety, and effectiveness will be derived from studies of at least one year's duration and evidence on harms from studies of at least three months' duration.

Settings

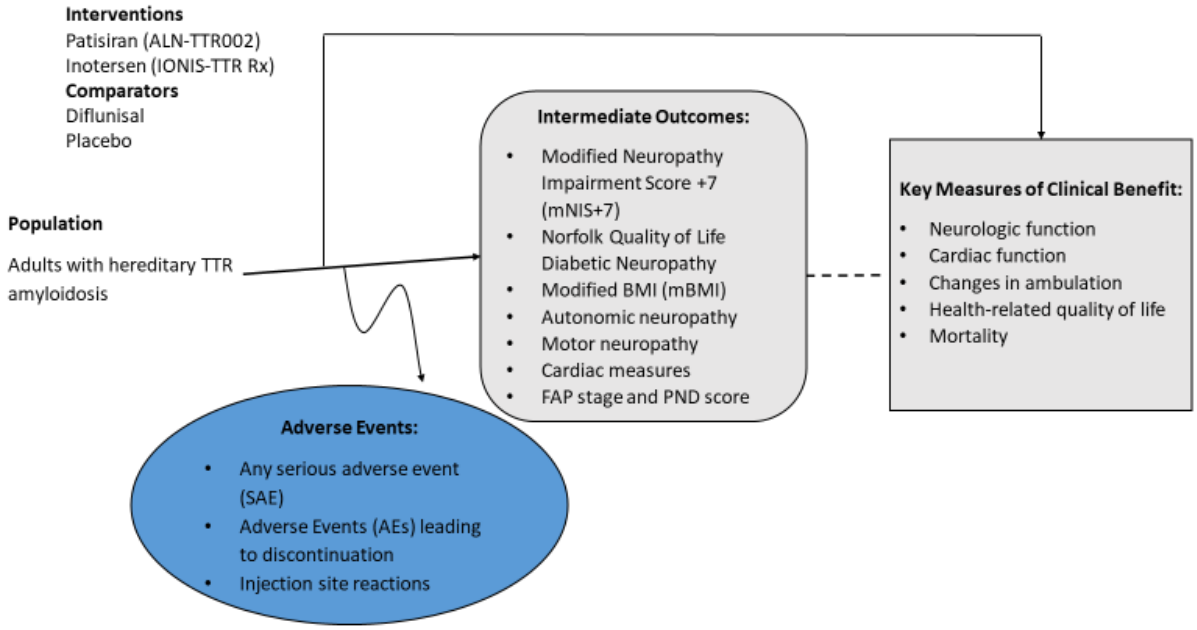
All relevant settings will be considered, with a focus on outpatient settings in the United States.

Study design

Randomized controlled trials and non-randomized controlled trials with any sample size will be included. Comparative observational studies of any size will also be included.

Analytic Framework

The proposed analytic framework for this project is depicted below:



The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific clinical or health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., change in mNIS+7), and those within the squared-off boxes are key measures of clinical benefit (e.g., health-related quality of life). The key measures of clinical benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of an action (typically treatment), which are listed within the blue ellipsis.

Evidence Review Methods

Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on patisiran and inotersen for hATTR will follow established best methods.[1,2] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[3] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search will be limited to English-language

studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We will include abstracts from conference proceedings identified from the systematic literature search. All search strategies will be generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Tables 1-2 below.

To supplement the database searches, we will perform a manual check of the reference lists of included trials and systematic reviews and invite key stakeholders to share references germane to the scope of this project. We will also supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Table 1: Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled trials

1	amyloidosis.mp.
2	patisiran.mp.
3	inotersen.mp.
4	ionis ttrrx.mp.
5	isis ttrrx.mp.
6	aln ttr02.mp.
7	rna interference.mp.
8	rnai therapeutics.mp.
9	antisense oligonucleotide.mp.
10	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	1 and 10
12	(animals not (humans and animals)).sh.
13	11 not 12
14	limit 13 to english language
15	(abstract or addresses or autobiography or bibliography or biography or clinical trial, phase i or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video-audio media).pt.
16	cohort studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/ or comparative study.pt.
17	control groups/ or (control* adj2 (clinical or group* or trial* or study or studies or design* or arm*)).ti,ab. or ("clinical trial" or "clinical trial, phase ii" or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or "multicenter study" or "randomized controlled trial").pt. or (random?ed adj6 (study or trial* or (clinical adj2 trial*))).ti,ab. or ((single or doubl*) adj2 blind*).ti,ab.
18	16 or 17
19	14 not 15
20	18 and 19

Table 2. Search strategy of EMBASE SEARCH

#1	'amyloidosis'	
#2	'patisiran'	
#3	'inotersen'	
#4	'ionis ttrrx'	
#5	'RNA interference'	
#6	'RNAi therapeutics'	
#7	'antisense oligonucleotide'	
#8	#2 or #3 or #4 or #5 or #6 OR #7	
#9	#1 AND #8	
#10	'animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp	
#11	'human'/exp	
#12	#10 AND #11	
#13	#10 NOT #12	
#14	#9 NOT #13	
#15	#14 AND [english]/lim	
#16	#14 AND [medline]/lim	
#17	#15 NOT #16	
#18	#15 AND ('chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)	
#19	#17 NOT #18	

Selection of Eligible Studies

Following the literature search and removal of duplicate citations using both online and local software tools, we will select eligible studies through screening at two levels: abstract and full-text. Two reviewers will independently screen the titles and abstracts of all publications identified using DistillerSR; a third reviewer will work with the initial two reviewers to resolve any issues of disagreement through consensus. No study will be excluded at abstract-level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

Data Extraction Strategy

Data will be extracted into DistillerSR. The basic design and elements of the extraction forms will follow those used for other ICER reports. Elements include a description of patient populations,

sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and quality assessment for each study (please see below). .

The data extraction will be performed in the following steps:

1. One reviewer will extract information from the full-text articles, and a second reviewer will validate the extracted data.
2. Extracted data will be reviewed for logic, and a third investigator will validate a random proportion of data for additional quality assurance.

Quality Assessment Criteria

We will use criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor."[4]

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.

Fair: Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.

Poor: Any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.

Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, we will scan the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include "patisiran", "ALN TTR02", "inotersen, and "IONIS TTRRx". We will select studies which would have met our inclusion criteria, and for which no findings have been published. We will provide

qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Evidence Synthesis

The purpose of the evidence synthesis is to estimate the clinical effectiveness of the interventions being compared. The analysis will be based on the data from all relevant studies identified from the systematic review. This section contains two components: (1) a summary of the evidence base and (2) a synthesis of outcome results.

We will synthesize all relevant evidence qualitatively. Data permitting, we will conduct quantitative analyses. Wherever feasible and appropriate, we will meta-analyze head-to-head studies of these interventions. If feasible and appropriate given the available evidence, we will also conduct network meta-analyses to add indirect comparisons (comparisons of interventions that have not been directly compared in head-to-head studies).

Summary of Evidence Base

Included studies will be summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the evidence base pertaining to the topic. An evidence table shell is presented in Appendix B. Relevant data include those listed in the data extraction section. Any key differences between the studies in terms of the study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), and study quality will be noted in the text of the report.

Synthesis of Results

For each outcome, all studies reporting results will be assessed for similarity in terms of the key characteristics specified in the data extraction section. The reported results from the studies that are sufficiently similar will then be checked to determine if the data are appropriate for analysis (e.g., sample sizes, number of patients experiencing the outcome, and point estimates with uncertainty estimates are reported as appropriate). Key considerations for interpreting the results within the context of the evidence base will be specified in the Evidence Report.

We expect analyses to be limited to those that are descriptive in nature only, as differences in entry criteria, patient populations, outcome assessments, and other factors are likely to preclude formal quantitative direct or indirect assessments of patisiran and inotersen, respectively, versus diflunisal. Nevertheless, if studies are sufficiently similar in terms of patient populations, outcomes assessed, interventions, and comparators, we will conduct random effect pairwise meta-analyses and network meta-analyses where feasible. A pairwise meta-analysis quantitatively synthesizes results from multiple studies that assessed the same intervention and comparator.[5] A network meta-analysis extends pairwise meta-analyses by simultaneously combining both the direct estimates

(i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator(s)). [6,7] The specific approach for any (network) meta-analysis will depend on the available evidence and will be detailed in the report.

References

1. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.
2. Higgins JP, Green S. *Cochrane Collaboration Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011].* The Cochrane Collaboration and John Wiley & Sons Ltd; 2008.
3. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *International journal of surgery (London, England).* 2010;8(5):336-341.
4. Agency for Healthcare Research and Quality. *U.S. Preventive Services Task Force Procedure Manual.* 2008.
5. Sutton AJ, Abrams KR. Bayesian methods in meta-analysis and evidence synthesis. *Stat Methods Med Res.* 2001;10(4):277-303.
6. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Statistics in medicine.* 2004;23(20):3105-3124.
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8. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Statistics in medicine.* 2010;29(7-8):932-944.
9. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *Bmj.* 2009;339:b2700.

Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2009.[3] Additional explanation of each item can be found in Liberati et al. 2009.[9]

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

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Appendix B. Data Extraction Summary Table Shell

Author & Year of Publication (Trial)	Study Design	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes